

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

FISCAL YEAR 1979

VOLUME 1

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

FISCAL YEAR 1979

Volume I

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ANNUAL REPORT

October 1, 1978 through September 30, 1979

National Institute of Neurological and Communicative Disorders and Stroke

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Fiscal year 1979 has been a year of contrasts and a year in which there have been important portents for the future. This was the first year that the NINCDS budget exceeded \$200 million (at \$212 million or an increase of \$34 million over FY 1978). The Congress indicated that much of the increase should go for support of individual investigator-initiated research grants (RO1's and PO1's). As a result, about 60 percent of approved competing grants have been funded (paying down to priority about 250). FY 1980 promises to keep pace with another increase to \$242 million proposed by the Congress. In terms of 1974 constant dollars, the 1980 level would for the first time put the NINCDS ahead of the FY 1974 appropriation by nearly \$4 million. Thus, in 1980 we would finally be able to catch up with inflation. The impact on the neuroscience research community is gratifying and long overdue. However, flexibility and discretion in the allocation of funds is fast disappearing. Again there have been essentially no increases for research training, for research contracts or for the intramural program. No relief is indicated in those areas for FY 1980, so that these elements of the NINCDS program are falling farther behind as inflation continues to take its toll. We can ill afford to have these trends persist.

Staff turnover and changes have been a major characteristic of FY 1979. Dr. Eldon Eagles, Deputy Director for three of the four NINCDS Directors, was forced to retire because of persisting ill health. He gave long and valued service and will be sorely missed. Dr. Murray Goldstein has been appointed as his successor. The turnover of all extramural program directors is now complete with the recent retirement of Dr. Kiffin Penry from the Neurological Disorders Program and its Epilepsy Branch. The new roster of program directors comprises: Drs. Floyd J. Brinley, Jr. (NDP) Eugene Streicher (FNP), Ralph Naunton (CDP), Michael Walker (Director-designate, STP) and John Dalton (EAP). Other retirements or resignations include Drs. Cosimo Ajmone-Marsan (Clinical Neurosciences Branch, IR), Carl Brewer and Maury Hanson (STP), George Murray (OPPE), and from the OD-NINCDS secretarial staff, Mrs. Lorraine Griffith, Mrs. Lee Jane Owen and Mrs. Shirley McNeil, replaced by Mrs. Beverly Surles and Mrs. Joan Ascencio. These and other staff changes reflect in part a mature 30-year-old Institute and the inevitable turnovers that that implies. The fact that the changes have been effected with a minimum of disruption and with good program continuities also reflects the health of the Institute and the dedication of its staff. We have been blessed with devoted and skilled people like those who have departed and those who have replaced them.

It is no longer easy or simple to recruit for or retain key staff. The Civil Service Reform Act, enacted at the beginning of the year; will introduce some major changes like the Senior Executive Service (SES) for the GS-16 or equivalents and above and the so-called Merit Pay System for the GS-13 to 15 groups. The DHEW has chosen to implement these "reforms" promptly, perhaps even, hastily. Preliminary evaluations of the SES and

Merit Pay Systems are far from encouraging in terms of retention, recruitment and equitable treatment for top management and research staff. The NINCDS has never been allowed to recover from the drastic cut in its personnel ceilings meted out in the early 1970's, and there is now so little flexibility in the NINCDS personnel system that the changes associated with the Civil Service Reform Act may prove particularly troublesome. Like most of the NIH Institutes the NINCDS is confronted more acutely each year by the problems of program changes and staff adaptations, especially in the Intramural Program. There is a pressing need for recognition and solution of this problem centrally and throughout the NIH.

Fiscal year 1979 has seen a number of significant Extramural Program developments. The Long-Range Strategic Research Planning process has been completed with publication of the seven panel-report volumes, plus the volume summarizing the public forum, a summary volume and an executive summary. These plans and research strategies have been distributed to the Congress, the Department and the community and are in use by the NINCDS staff as guides to forward planning.

The favorable funding situation has made it possible for the positron emission transverse tomography (PETT) program to be implemented with some \$5 million worth of research grant awards for five centers. Another center and the NINCDS Intramural PETT facility will be started shortly. We regard the PETT program as a particularly important initiative because of its potential to elucidate many basic and clinical problems of central nervous system metabolism and function. The FY 1979 appropriation also made it possible to begin to deal with the remainder of the implementable recommendations of the Epilepsy and the Huntington's Disease Commissions. In addition, development of comprehensive stroke and comprehensive trauma centers and of stroke and coma data banks continues. The many other Extramural Program developments are detailed in the annual reports by the respective program areas.

The NINCDS has made a major decision about the direction of its scientific information programs. The literature retrieval system developed with the NLM for investigators in the communicative sciences and disorders has been successfully launched. After careful evaluation of the Brain Information Service for the neurosciences, the NINCDS, in concert with its advisors, has decided to terminate its support and to substitute a neuroscience citation retrieval system developed with the help of NLM personnel. The neuroscience system is now ready for introduction into the neuroscience research community, with a demonstration exhibit scheduled at the November annual meeting of the Society for Neuroscience. As noted in the 1979 report to the Senate Appropriations Subcommittee for Labor-HEW, the Brain Information Service has been an excellent traditional approach to neuroscience information needs, but now there are more effective, versatile and individualized approaches available that utilize the NLM and regional library computerized data base facilities reaching over 1000 libraries around the country and the world.

International activities continue at modest but wide-ranging levels, mostly in relation to the World Health Organization's Collaborating Centers Program for Research and Research Training in the Neurosciences. The NINCDS

has viewed its role, as one of the designated collaborating centers, to provide staff expertise, since commitments of major funds have not seemed feasible or appropriate. Thus, NINCDS staff have participated during FY 1979 in the neuroepidemiology planning workshop at Dakar (Senegal), in developing the protocol for a multi-country collaborative trial of a new drug for diabetic neuropathy; and in training courses for neurologists at the Marseille (France) center and for public health nurses at the Ibadan (Nigeria) center. The NINCDS Director travelled as a member of a three-man WHO team to visit the People's Republic of China in July. We toured the principal neurological and neurosurgical centers in Peking, Tientsin and Shanghai. We found a very high level of clinical expertise, much interest in research, and a clear potential for collaborative studies. A detailed report of this trip has been prepared for wide dissemination.

The NINCDS Intramural Program continues to be a special source of scientific satisfaction. It is staffed by many gifted investigators and it is characterized by a number of exciting and innovative basic and clinical projects. Many of the projects are described in detail in the accompanying reports. Here only a few can be mentioned as examples: New applications of tissue culture techniques to provide specific types of neurons or to correlate brain tumor cell responses to chemotherapy with the clinical course; neuroimmunological approaches to the multiple sclerosis problem, with isolation of a specific measles protein, with studies of the immunoresponsiveness of twins with MS, and with myelin changes in relation to disease progression; viral studies to provide animal models for herpes encephalitis, papova virus-induced brain tumors and fetal hydrocephalus induced by cytomegalovirus and to provide an understanding of the molecular basis for the production and actions of defective interfering viral particles; refinements in enzyme replacement therapy to better attack the lipid storage diseases; continued progress in delineating the roles of peptide transmitters, modulators and hormones in the nervous system; and innovative techniques of electron microscopy to elucidate the mechanism of neurotransmitter release and the interactions of viral antigens with host cellular immune systems.

Like our extramural programs, the NINCDS Intramural Program is facing major program and staffing challenges. Several laboratories have been closed as their principals moved to other activities, and the direction of other laboratories or branches will change when recruitment of new chiefs can be accomplished. With the acquisition of a cyclotron facility (now approved by the NIH) an intramural PETT program will soon become a reality. Plans for collaborative studies with NIMH and NIA groups are already in being and additional studies from NCI and NHLBI are anticipated. With completion of the Ambulatory Care Research Facility only about a year hence, active planning for NINCDS programs and facilities therein must assume high priority. A major initiative is contemplated for a Communicative Disorders Branch, and recruiting of key personnel to staff the branch and plan its programs will be undertaken shortly. Resources for intramural research are a perpetual problem, but the one resource which is most troublesome is personnel. For a decade now, the NINCDS has been badly constrained in this respect, so that the NINCDS Intramural Program faces acute needs for some 30 or more key staff to fill existing positions and to provide for

the PETT program and Communicative Disorders Branch. Moreover, the pools of young clinical and research associates remain at minimal levels and must be replenished if we are to extract the maximum yields from our intramural endeavors. This is a unique and extraordinarily productive component of the NINCDS research programs. It needs nurturing at this time.

All components of the NINCDS programs are heavily dependent upon advice and counsel from the biomedical research community and interested and knowledgeable lay people. This is true not only for our National Advisory Council and our Board of Scientific Counsellors but also for our extramural programs as well. We continue to be frustrated by the unwillingness of the administration to provide the NIH with adequate peer review groups for research grant applications and especially for research training applications and to provide the NINCDS with the program advisory committee charter(s) that it must have. Each program operates with an ad hoc group, but this ignores both sides of the law, which requires on the one hand external advisors to conduct concept reviews and on the other requires such groups to be duly chartered. This absurd situation would be laughable if it were not for the seriousness of our dilemma in trying to develop programs and to invest funds as wisely and effectively as possible. Moreover, we are being asked, quite properly, to emphasize affirmative action and civil rights compliance for recruitments of minorities and women into advisory groups as well as into the Institute staff. Without more realistic personnel and advisory committee policies, EEO commitments can hardly flourish.

During FY 1979 the NIH and much of the rest of DHEW were directed by the Secretary to develop a series of health and health research planning principles. Drafts of these principles have now been circulated. Surely they reflect many important needs for the future, but they do not address the problems of research training and they give relatively little attention to some of the most devastating and costly disabilities which face this nation, namely, the neurological and communicative disorders.

In late FY 1978, a small group of neuroscientists met at the behest of Dr. Fred Plum, a member of the NANCDS Council, to consider the Secretary's request in the context of the neurosciences and the neurological and communicative disorders. Their deliberations were forwarded to the appropriate committee, but because the final documents appear not to address some of the important issues raised by the Plum group, I think those issues deserve reiteration here as having particular relevance in the current fiscal and manpower climate for research.

The Plum group argues that "man's efforts to understand his own brain represent the greatest scientific challenge of our time [and] also represent his loftiest humanistic concerns." In this context their first emphasis is on stability of research support, which should include a more realistic percentage of total health expenditures, creation of liquid reserves to buffer funding fluctuations, recognition of outstanding research laboratories by commitments for long-term support, and more generally a shift to 5-year funding for meritorious long-range research programs.

Secondly, priority should be given to research on biological bases of behavior to deal with major problems in cognitive, behavioral and mental disorders--all uniquely human disorders.

Thirdly, funds should be appropriated to correct the deterioration and obsolescence of research facilities and equipment, with emphasis on interdisciplinary opportunities among biological and physical scientists and engineers. Moreover, appropriate mechanisms should be developed to foster interdisciplinary technological transfers.

Next, the selection of Study Section and Advisory Council members should be based on non-political considerations of merit, only and should be exempt from current limitations on numbers and sizes of such units. In addition BID's should consider development of research planning boards to advise on identification of promising research areas likely to result in major discoveries and to influence favorably future health care, and thus aid in the allocation of scarce and expensive resources.

A fifth emphasis is to assure ample opportunities for young investigators by re-initiation of a training grant program and by continuation and expansion of the Research Career Development type of awards. The latter should include special attention to the recruitment, training and retention of the clinical investigator. All such awards should be accompanied by small research grants and by appropriate stipend adjustments.

Additional emphasis is given to interdisciplinary research at all levels both basic and clinical and to the purpose of basic research, namely the prevention of disease. Because there are no simple or rapid solutions to understanding nervous system function or preventing devastating neurological disorders, relatively expensive halfway technologies may be needed, but these must be viewed as stopgap measures that only ameliorate symptoms and leave causes untouched.

Finally, the group concurred in the view that DHEW-supported research must develop knowledge that supports all health missions of the Department but pleads that the energies of the NIH not be diverted from its fundamental mission to provide the research basis upon which all future health care must depend. Thus, knowledge about synaptogenesis and synaptic modifications and modulations may lead to prevention or modification of such major disorders as mental retardation, pain and dementia and to development of effective sensory prostheses in the deaf and the blind. Likewise, understanding of cortical neuronal networks may provide the keys to thought and memory, to the synthesis of skilled movements, and to the translation of the experience of sensory receptor input into behavior and the sense of self.

On the threshold of its 30th year, the NINCDS is fortunate indeed to have the benefit of the support and counsel of such thoughtful experts and to have enlisted the enthusiastic and fruitful research of so many neuroscientists both basically and clinically oriented. We are making inroads on the difficult disorders of the nervous system, but the arguments summarized here must be heeded if we are to continue the progress so boldly begun.

ANNUAL REPORT
October 1, 1978 through September 30, 1979
Equal Opportunity Office
Office of the Director
National Institute of Neurological and
Communicative Disorders and Stroke

One of the major program priorities of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is to continue to implement an effective Affirmative Action program that will produce results.

In Fiscal Year 1979 we were successful in placing minorities and women in such areas as the Administrative Officer series, Health Scientist Administrator, Search Committees, Postdoctoral Research appointment and the Summer Employment Program. However, as seen by the May 1979 report on the Status of Minorities and Women at NINCDS, there still is underrepresentation of minorities in the Biologist, Chemist and Microbiologist job series. There are no minority women in Staff Positions GS-12 and above, special recruitment initiatives are needed to correct the underrepresentation of Hispanics and American Indians and we need to increase the representation of minorities and women in top level positions in the Institute. To correct those areas where an imbalance of equal opportunity exists, the Institute is developing Affirmative Action goals and initiatives for Fiscal Year 1980 that will bring about representation of minorities and women at all levels of management in the NINCDS.

Some Affirmative Action Initiatives and Accomplishments for FY 79 were:

1. A minority was appointed as the Administrative Officer for the Neurological Disorders Program, Fundamental Neurosciences Program, Communicative Disorders Program, and the Office of Biometry and Epidemiology.
2. A minority was appointed Acting Chief, Scientific Evaluation Branch, Extramural Activities Program.
3. Minorities and Women were appointed to NINCDS Search Committees.
4. A pamphlet describing the various opportunities for minorities and women in biomedical research at the NINCDS was developed and distributed to minority and women scientists, health professionals, and the general public. Another pamphlet describing summer employment opportunities for minority and women students in biomedical research was prepared and distributed to minority and women students and school.
5. Two women were added to the Administrative Officer series (341).
6. The NINCDS and the Division of Personnel Management, NIH, sponsored a workshop for high school and college counselors in the metropolitan

areas of Maryland, Virginia, and the District of Columbia. The workshop focused on areas that would assist school counselors in advising students on career opportunities in the Federal Government.

7. A minority was selected for a Postdoctoral Research appointment in the Institute's Intramural Research Program.
8. Three Minority Biomedical Support Program Projects were approved for funding by the Institute's National Advisory Council.
9. A woman was appointed Deputy Director for the Neurological Disorders Program.
10. Another minority was selected as a Health Scientist Administrator in the Extramural Activities Program.
11. The Institute participated in the Minority Biomedical Symposium in Atlanta; the Minority Access to Research Careers Program Director's Meeting in Dallas; and the National Medical Association Conference in Detroit.
12. In May the Institute sponsored a Women's Week Program for its Staff. The Program focused on areas concerning women in the Federal Government.

With the establishment of an Affirmative Action Outreach Program, the Institute made significant progress in the recruitment and placement of minority undergraduate, graduate and medical students for the summer employment program. Three Black medical students and six minority undergraduate students were selected for positions in the Institute's Intramural Research Program and the first Black journalism student was selected as a Writer-Editor in the NINCDS Office of Scientific and Health Reports. Plans are being developed to expand this Affirmative Action Initiative in order to increase the representation of Hispanics and American Indians.

The Institute continues to maintain a strong commitment to increase the participation of minority and women scientists and students in basic clinical research and research training in the neurological and communicative sciences, specifically: (a) The Institute in March 1979 established a cooperative agreement with the National Institute of General Medical Sciences to support elements of the Minority Access to Research Careers Program (MARC). The agreement extends support to minority institutions and to individuals attending minority institutions under the MARC program to include activities with relevance to the research and training programs of the NINCDS. This gives an opportunity to an increased number of minority scientists to participate in research and research training in fields of research supported by the NINCDS, and (b) agreed to support and participate in the proposed conference and workshops for Minority Biomedical Support Program Grantee Institutions.

Finally, realizing the Institute's responsibility in the enforcement of

the Civil Rights Act in matters concerning its contracts and grants the NINCDS in FY-79 implemented the following actions:

1. Program Directors will make sure that institutions which have or may seek NINCDS training grants and contracts are aware of and sensitive to the Institute's Affirmative Action goals and initiatives to promote stronger involvement of minorities and women in the neurological and communicative sciences.
2. Training grant application instructions and information brochures will state clearly the Institute's position and support of Affirmative Action and to encourage the recruitment of minorities and women trainees, and
3. During visits to grantee institutions staff members will inform Administrators and Investigators of the Institute's Affirmative Action position.

The results of these properly tailored Affirmative Action approaches will produce, in our opinion, a pool of minorities and women scientists with expertise in the Neurological and Communicative Sciences.

ANNUAL REPORT
October 1, 1978 through September 30, 1979

Office of Scientific and Health Reports
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) information, publications, press, and public affairs activities are centered in the Office of Scientific and Health Reports (OSHR). The Office consists of two established sections, Public Inquiries and Publications, with a third section being developed for public affairs and media relations.

OSHR advises the Director and executive staff on the effective interpretation and reporting of Institute-conducted and supported research. This research is of interest and concern to many audiences, including Congress, the Department and other agencies of government, scientists, physicians, voluntary health agencies, patients and their families, and the general public. The Office initiates projects designed to convey public and scientific information to these audiences, and responds to Congressional, Departmental, NIH, internal, and public requests for information.

Coordinating the NINCDS research program with the programs of some 48 private voluntary agencies and 35 professional societies is a major OSHR function. This work was expanded in Fiscal Year 1979 with inauguration of RESEARCH CURRENTS -- an information kit for voluntary agencies. Sent three or four times a year to agency directors and editors of agency newsletters, the kit contains brief reports of current research conducted and supported by NINCDS, copies of new NINCDS publications, summaries of recent meetings, news clips, and other information useful to the agencies and their members. Each issue of the kit is accompanied by a letter from the NINCDS Director touching on topics of general current interest.

Many other regular services to voluntary agencies continued in 1979. These included publication of an annual directory of the agencies, meetings with agency representatives to provide public information advice and to discuss ways to share and disseminate information, and supplying publications for voluntary agency meetings and general distribution.

New efforts were undertaken this year to share with the voluntary agencies information about publicity opportunities, and to offer NINCDS staff members as speakers for their programs. Initial contacts were made which may lead to NINCDS participation in nationwide telethons on behalf of the Muscular Dystrophy and Cerebral Palsy Associations. Also, agencies were alerted to reporters preparing stories on their disorder; one resulting piece -- a major feature story on multiple sclerosis in NEW YORK magazine -- was read into the CONGRESSIONAL RECORD, as suggested by

an OSHR staff member. The plan is to extend this type of information sharing and cooperation to all voluntary agencies concerned with neurological and communicative disorders.

As for the past 23 years, OSHR again prepared special reports on disorders designated by the House Subcommittee on Appropriations. These state-of-the-art reviews describe the disorder and the Institute's research program to counter it; report research advances of the past year, including any new developments in therapy; and briefly project the outlook for the future. This year, seven special reports were prepared: Amyotrophic Lateral Sclerosis; Epilepsy; Huntington's Disease; Multiple Sclerosis; Hearing, Speech and Language; Spinal Cord Injury; and Stroke. All were written by OSHR staff members. OSHR also contributed material on genetics and diabetes to special reports of the National Institute of General Medical Sciences and the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Efforts to reach physicians and other health care personnel were strongly pursued in 1979. Besides an expanded exhibit program (see Public Inquiries Section), OSHR continued to produce NINCDS Notes, a monthly news service for journals of neurology, neurosurgery, otolaryngology, speech, and the neurosciences. NINCDS Notes averages approximately four pages of copy, and covers program and administrative developments in the Institute. The audience is primarily heads of departments, chairmen of training programs, grantees, potential grantees, and clinicians. This year, NINCDS Notes introduced more detailed reporting of NINCDS-sponsored meetings, including reports of a slow virus workshop and a symposium on brain peptides. Reports of such meetings are also made available to physicians through the NIH RECORD, which over the past year published an increased number of stories about NINCDS activities.

The Institute's media relations effort was greatly strengthened in Fiscal 1979 by the assignment of a staff member full-time to this function. Coverage was increased many-fold in both print and electronic media (see Media Relations Section).

In cooperation with the NIH Audiovisual Branch, OSHR helped develop public service announcements encouraging parents to check for hearing loss in their young children. At the end of the fiscal year, a 30-second TV spot is ready for distribution, as are three radio spots of varying lengths. Plans are under way to develop similar public service announcements to teach the signs of stroke.

OSHR helped the Institute meet its Equal Employment Opportunity goals by recruiting NIH's only black summer intern in public information. That OSHR is well regarded within the NIH information community is demonstrated by the NIH Training Committee's request that we accept a full-time intern for 9 months' training under the NIH Public Information Internship Program. This intern will join OSHR in September 1979.

To improve service to the Hispanic communities, OSHR this year located a Mexican-American specialist in broadcasting and public information, and nominated this woman for appointment to the NINCDS Science Information Program Advisory Committee.

Scientific Publications Section

The Scientific Publications Section produces and distributes publications for the general public and for a variety of scientific and professional audiences. The Section serves various administrative units of the Institute, ad hoc committees preparing reports, and outside organizations in the neurological and communicative disorders fields. The services include planning, clearance, writing, and editing of publications; securing design, layout, and printing; distributing and storing publications; and subsequent revision and reprinting according to demand. The Section works with the NIH Printing Unit, the Medical Arts and Photography Branch, and the Government Printing Office in producing publications, and also serves as the Institute's supply center for these materials.

The Institute's Monograph Series continues, with 23 titles to date, 13 of which are still in print. Two new monographs were published in Fiscal Year 1979: The Neurological Bases of Language Disorders in Children: Methods and Directions for Research, and Workshop on the Neurological Basis of Autism. Two scientific bibliographies, Valproic Acid: A Classified Bibliography with Keyword and Author Indexes and Antiepileptic Drug Serum Concentrations: Clinical Value and Methodology, were printed and made available, and bibliographies on kuru and Creutzfeldt-Jacob disease were produced. The Section handled a 2-volume publication for the Communicative Disorders Program titled Medline Users Manual and Thesaurus for Specialists in Communicative Disorders. OSHR also handled editorial printing services for the Institute's largest scientific publication project of the year -- the 12-volume National Research Strategy for Neurological and Communicative Disorders.

At the request of the concerned voluntary health agencies, the Section printed new fact sheets on narcolepsy, autism and tuberous sclerosis. Section staff members worked closely with representatives of the voluntary agencies in writing, editing, and distributing these fact sheets.

Near the close of the fiscal year, new Hope Through Research (HTR) pamphlets on Huntington's disease and aphasia were in press, and a new pamphlet on epilepsy was being prepared. HTR pamphlets continue to be popular with the general public, especially when they are promoted through media stories. An article in PARADE magazine about brain tumors, for example, produced a glut of requests for the HTR pamphlet on this subject. An intensive effort to improve the series is planned for the new fiscal year. OSHR has been authorized the services of an expert consultant writer/editor who will devote full attention to the task of determining the public's needs (including special needs of black and

Hispanic communities), identifying unused but effective methods of distribution, introducing new pamphlets and updating old ones, and improving the appearance and appeal of the series.

A variety of miscellaneous pamphlets and documents were produced, including a much-needed pamphlet on stroke prevention, a guide to NINCDS extramural programs, and documents describing intramural and extramural training programs. A booklet on summer employment opportunities for minority and women students was prepared. Seven special reports to Congress on major research program areas were printed, and the first issue of what will be an annual NINCDS Fact Book was published.

Public Inquiries Section

The Public Inquiries Section responds to written inquiries and telephone calls concerning research findings on some 600 neurological and sensory disorders. Many of the inquiries involve difficult subject matter, and staff members must coordinate closely with intramural scientists and grantees before fully factual responses can be written. Likewise, policy inquiries require close interaction with the NINCDS Office of the Director, Institute program directors, and the NIH and HEW Secretariat.

Inquiries addressed to the NINCDS are not confined to research; they also cover patient care, rehabilitation, health care services, and the economics of neurological and sensory disorders. For complete answers to these inquiries, staff members must obtain pertinent information from other components of the Department, other agencies of Government, and from state agencies through which services and financial aid are funneled.

Last year 818 individually prepared responses were sent to the Institute's lay and medical audiences. Another 147 responses to controlled letters from the Congress and the White House were written and coordinated with the NIH Secretariat. Many other inquiries were answered with printed materials. In all, NINCDS responded to requests for over 222,846 publications, including 102,355 Hope Through Research pamphlets, 96,650 fact sheets, 4,994 monographs, and 32,453 miscellaneous publications.

Responsibility for scheduling and staffing the Institute's exhibit rests with the Public Inquiries Section. This year, two new portable exhibits were designed and the exhibit schedule was expanded to reach new audiences of primary practitioners and minority members of the health professions. In Fall 1978, the exhibit was displayed at the American Academy of Ophthalmology and Otolaryngology meeting in Las Vegas and the Society for Neuroscience meeting in St. Louis. In the first 6 months of 1979, the exhibit was taken to meetings of the American Academy of Neurology in Chicago; Minority Biomedical Support in Atlanta; the American Laryngological, Rhinological, and Otological Society and the American Association of Neurological Surgeons, both in Los Angeles; the American College of Physicians (ACP) in San Francisco; and the National Medical Association

in Detroit. Taking the exhibit to the ACP meeting was a pilot effort to test the receptiveness of primary physicians to information about neurological disorders. Response was encouraging.

This year saw the start of a fledgling information effort aimed specifically at NINCDS personnel. As NINCDS activities become more visible in the media, staff members expressed an interest in learning about stories or TV/radio appearances of other NINCDS staff. But because NINCDS offices and laboratories are scattered throughout several buildings, many staff members were unaware of growing public interest in their work. NINCDS CLIPS was introduced to help solve this problem. An extension of the bulletin board located near the Office of the Director, NINCDS CLIPS is prepared in the Public Inquiries Section; it is a pasteup of newspaper and magazine articles, printed in poster form so it can be put up in offices throughout the Institute. Also, OSHR now sends special notices to all NINCDS offices whenever a staff member will be appearing as a guest on radio or television.

The Public Inquiries Section provides materials for the Institute's Advisory Council meetings, updates the Council Directory, and plans the annual Council dinner. The head of the Section also serves as information liaison with the Extramural Activities Program and with the Program Directors in the Federal Building; she is responsible for identifying grantee research appropriate for use in Institute reports and publications, and writes annual special reports for Congress on cerebral palsy and spinal cord injury.

The head of the Section also serves as the focal point for discharging Institute responsibilities under the Freedom of Information Act. This year the Section responded to 52 requests for summary minutes of the meetings and to 111 requests for substantive information about the Institute's programs, including an extraordinary request from Friends of Animals for complete--and often voluminous--files on 78 grants.

Media Liaison Section

The newly established Media Liaison Section responds to inquiries from representatives of the news media, issues news, supports special events, and develops media interest in the broad range of activities carried out by NINCDS.

Last year, the Section's first year of operation, local and national coverage of NINCDS activities included 68 appearances in print, 41 in television, and 46 in radio. Highlights of the year's achievements include placement of a front page story on stroke research in the WALL STREET JOURNAL, articles in the NEW YORK TIMES on slow virus research, and brain peptides, a story about spinal cord injury treatment in TIME, a dramatic two-page story, "Anatomy of a Stroke," in LIFE, and two stories in PARADE magazine--one on Huntington's disease research, the other on brain tumors. Through these publications alone, the NINCDS

story reached millions of readers. And while stories about specific diseases--particularly stroke and epilepsy--remain popular with writers, we are also encouraged by the interest shown in basic brain and nervous system research. Attempts are made to kindle enthusiasm in scientists' efforts to chart the unknown, so that the public will more easily appreciate the subtle but often provocative nature of biomedical research.

NINCDS laboratories were filmed for the CBS-TV pilot science program, "Universe," hosted by Walter Cronkite, and two NINCDS scientists were guests on "Good Morning America," discussing research involving obstetrical anesthesia. In September, an NINCDS scientist appeared on Hugh Downs's "Over Easy" to discuss Parkinson's disease. Besides these national appearances, NINCDS staff members were guests on several TV and radio programs within Washington, D.C., including PANORAMA and FUTURE FILE (part of the Channel 9 Evening News).

In some cases the impact is magnified. Some news stories prepared locally are eventually carried by a syndicate or wire service and certain locally produced TV pieces on NINCDS have been picked up by network affiliates nationwide.

In this first year, emphasis has been placed on developing good rapport with editors and writers to establish the mutual trust that will pay dividends in the future. The Section head has visited editors and writers at many major publications to offer story ideas and encourage understanding of the Institute's mission. Reporters occasionally visit OSHR, and interviews with NINCDS scientists are arranged on request. The Media Relations Section receives excellent cooperation from NINCDS staff at all levels.

This year, the Section began work to improve media coverage of NINCDS involvement in medical meetings. Careful advance work and on-the-spot liaison with media have produced excellent results in areas where NINCDS was little known. For example, during the Second International Huntington's Disease Symposium in San Diego, OSHR placed feature stories with both major local newspapers and on three TV news broadcasts, and provided guests for radio and TV talk shows. During the April 1979 meeting of the American Association of Neurological Surgeons, an NINCDS-related story was placed with the LOS ANGELES TIMES.

Future plans call for more coverage of extramural activities and increased cultivation of the minority media.

Besides established media outlets, opportunities to tell the NINCDS story have been found in unexpected places. Through contacts OSHR made with Friends of the Kennedy Center, the NINCDS director became the first NIH scientist to participate in a radio talk-show, "From the Kennedy Center," broadcast from the stage of the Eisenhower Theatre. Also a guest on this program was Arthur Kopit, author of WINGS, a new play about a stroke victim. Playwright and scientist discussed the effects

of stroke, and the special problems involved in overcoming aphasia.

The effectiveness of OSHR is bolstered by a creative, team approach to public information. While each Section has its own responsibilities, the work frequently overlaps and results achieved by one Section will reverberate in another. When the Media Liaison Section successfully places a story about NINCDS research in an important newspaper, for example, the result is an increase in public requests for more information about a subject. From these requests, the Public Inquiries Section may identify the need for a pamphlet not in the NINCDS portfolio, and that information will be shared with the Publications Section, which will investigate ways to meet the need. From our achievements this year, it is obvious that there is a substantial and expanding market for information about neurological and communicative disorders.

Most vital to our work is the cooperation of other Institute staff members. Our experience this year makes us believe that NINCDS staff members are becoming more aware of the value of public information, and are willing to participate when called upon. This positive approach is due in large measure to the strong support provided the public information function by the NINCDS Office of the Director.

ANNUAL REPORT
October 1, 1978 through September 30, 1979

Office of Program Planning and Evaluation
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

The Office of Program Planning and Evaluation (OPPE) serves as principal advisory and support staff to the Director of the Institute on program development, analysis, program evaluation and the development of strategic and operational program plans. The Office provides staff support to facilitate the integration of the program planning, analysis and evaluation efforts in the categorical program areas and provides the Director and the Executive staff with assistance in coordinating the development of goals of the Institute programs and strategies for meeting these goals. The Office has developed, with the staffs of program areas of the Institute, a process to prepare annual implementation plans which form the basis for resource allocation decisions and a development of the Institute's Research and Legislative Plan and budget requests for future years.

This recently developed planning process offers an opportunity to all programs within the Institute to provide a comparable input about program needs, research opportunities, priorities, etc., in a uniform fashion for use in resource allocation decisions by the Director. On the basis of these submissions, discussions and negotiations, OPPE develops an Institute operational plan which documents agreements on approved program initiatives and resource apportionment to carry out the Institute programs for the coming year. During the past fiscal year this multi-year plan formed the basis for development of the Research and Legislative Plan, which the Institute is required to submit to NIH/PHS annually.

In FY'79 the Office coordinated the development and publication of the Institute's long-range research strategy as a consciously articulated framework within which the annual program planning can take place. This document entitled the "National Research Strategy for Neurological and Communicative Disorders," summarizes the findings of seven categorical expert panels and their recommendations, and, articulates Institute goals for the next decade, which encompass and respond to panel findings and recommendations.

The Office has been a focus in coordinating the development of special reports and issuing papers concerning the Institute's program efforts in specific areas of special interest to NINCDS and NIH. During the past fiscal year the Office coordinated the development of Institute policies and positions on a number of scientific issues. This included NINCDS support of research related to neuroendocrinology, National Toxicology Program, rehabilitation, nutrition, primary and secondary prevention, life styles, environmental health, environmental causes of morbidity and mortality, technology transfer, other ad hoc requests, and draft legislation related to in vitro screening and testing. In addition, the Office participated in the development of research classification systems such as BAD (Basic, Applied and Developmental Research),

SATT (Science Base, Applications Research, Technology Transfer and Training), clinical trials, etc., and coordination of reporting the Institute's research activities in terms of these classification codes. The Office provided representation of the Institute at the Inter-Institute Coordinating Committees on Diabetes, Nutrition, Digestive Disorders, and Arthritis, speaking for the Institute from a knowledge of its programs, policies and positions, and provided these groups with the professional judgments related to review and analysis of subject areas of interest to them.

The Office has central management focus for the Institute's science information programs, which provides summarized literature review and bibliographic references to the research and clinical community in fields related to the Institute's mission. This year the Office, in collaboration with the National Library of Medicine, has developed a number of search strategies for specific neuroscience topics using the SDILINE (Selective Dissemination of Information). "Stored Search" capability, which produces automatic printout of citations of personal interest from the current input to MEDLINE, is also emphasized. An announcement on the availability of these enhanced services will be out soon.

As a legislative focus for the Institute, the Office continued to work with appropriate staff of OD/NIH to keep in touch with and to monitor the process of legislation in order to safeguard and clarify the legitimacy and appropriateness of the Institute's mission.

The Office has continued the development of an integrated Program Information System for the Institute. This will combine programmatic, fiscal and management data into an integrated Institute-wide data base. During the past year, two contracts were awarded, one for the development of computer programs to fulfill the management requirements and the other to validate and install the programs developed by the other contractor.

Research Projects: Work on the six research projects, which were listed and described in the Annual Report for Fiscal Year 1978, has not progressed during this fiscal year. For this reason no PHS-6040 forms with detailed descriptions for these research projects are included in this Annual Report for Fiscal Year 1979. Progress in these research efforts will be duly reported in future Annual Reports as data resources gradually become available.

The principal investigator for these studies is Zekin A. Shakhashiri, M.D., Deputy Chief, OPPE. The titles of these research projects are: (1) Study of Mental Retardation; (2) Public Health Implication Study; (3) Study of Labor (in collaboration with NICHD); (4) A Study of Comparative Health; (5) Comparative Schools of Thought in Medical Science and Practice (A Study in Medical Care); and, (6) Administrative Research (in collaboration with NICHD).

CONTRACT NARRATIVE
Office of Program Planning and Evaluation, NINCDS
Fiscal Year 1979

NINCDS PROGRAM INFORMATION SYSTEM (PINS) (NO1-NS-8-2301), JRB Associates, Inc., 8400 Westpark Drive, McLean, Virginia 22101.

Title: Validation and Technical Support-NINCDS Program Information System

Contractor's Project Director: Laurence C. Novotney

Allocation: \$261,455

Objectives: The contractor is to: 1) provide technical support to the Institute by coordinating the definition, initialization and creation of the data base; 2) assist in the selection and placement of peripheral hardware throughout the Institute; 3) assist the Office in establishing procedures to ensure the efficient and secure operation of the System upon installation; 4) sequentially validate the PINS data and computer programs as they are released by the programming contractor; 5) review validated products with the appropriate members of the NINCDS staff; and 6) train Institute staff in the use of the system, type of output available and the interpretation of various report formats.

Major Findings: This contractor has developed the orientation guidelines for the programming contractor. The programming contract is expected to be awarded in September '79.

Significance to the Program of the Institute: The scientific and program information concerning grant, contract and project management, financial (e.g., budget and operating expenses) program projection requirements, and personnel continue to increase in size and complexity. Therefore, rapid access to pertinent facts on a timely basis is essential for effective management. By utilizing a data base management system (DBMS) which provides controlled access to the Institute-wide data base, and programming, maintenance and operations will be simplified and PINS will meet this need and make data accessible when and where it's needed, and in a form that can readily be used. In addition, the PINS will maintain data currency, validity and compatibility between it and existing NIH systems such as IMPAC, CAS, CRISP, etc.

Proposed Course: The contractor will be conducting orientations, briefings, and reviews of technical documentation with the programming contractor to ensure their correct understanding of and compliance with the PINS specifications; collecting and converting initial manual and automated data from sources which are located both inside and outside the NINCDS for inclusion in the PINS data base; and coordinating the automated transfer of data between the PINS and those systems supported by organizations external to the NINCDS.

CONTRACT NARRATIVE
Office of Program Planning and Evaluation, NINCDS
Fiscal Year 1979

NINCDS PROGRAM INFORMATION SYSTEM (PINS) (N01-NS-6-2345), JRB Associates, Inc., 8400 Westpark Drive, McLean, Virginia 22101.

Title: Design and Specifications for a NINCDS Program Information System (PINS)

Contractor's Project Director: Laurence C. Novotney

Allocation: \$33,000

Objectives: To develop a system design to support the efficient input, storage and retrieval of the scientific and programmatic data required to effectively plan, analyze, evaluate, and manage program activities at all levels of the NINCDS.

Major Findings: The contractor revised the detailed programming specifications for the PINS, as a result of experience gained during the Intramural Research Management Information System (IMIS) development phase. In addition, the contractor reviewed these final specifications to identify changes in Institute requirements, existent errors and alternate approaches to programming techniques to enhance development and/or operation of the system. In addition, the contractor provided the support to analyze, develop and evaluate additional information requirements of the NINCDS.

The contract terminated July 31, 1979.

Significance to the Program of the Institute: The scientific and program information concerning grant, contract and project management, financial (e.g., budget and operating expenses) program projection requirements, and personnel continue to increase in size and complexity. Therefore, rapid access to pertinent facts on a timely basis is essential for effective management. By utilizing a data base management system (DBMS) which provides controlled access to the Institute-wide data base, programming, maintenance and operations will be simplified and PINS will meet this need and make data accessible when and where it's needed, and in a form that can readily be used. In addition, the PINS will maintain data currency, validity and compatibility between it and existing NIH systems such as IMPAC, CAS, CRISP, etc.

Proposed Course: The work on the JRB contract has been favorably received; therefore, the Institute is awarding contracts for the next phase, i.e., development of computer programs, their validation, and installation of PINS.



ANNUAL REPORT

Office of Biometry and Epidemiology, OD
National Institute of Neurological and Communicative Disorders and Stroke

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Annual Report
for Period October 1, 1978 through September 30, 1979
Office of Biometry and Epidemiology
Office of the Director
National Institute of Neurological and Communicative
Disorders and Stroke

The Office of Biometry and Epidemiology (OBE) supports a program in biostatistics, field studies and computer science to further medical research in the areas of neurology and communicative disorders.

The Office is active in a number of specific program areas, which it plans to continue on a level without significant expansion in FY 1980. Given the availability of additional research funds, OBE will propose new areas of activity for FY 1980. In addition, as present pilot studies give way to national studies, and as consensus meetings anticipate full-fledged studies, expansion of present programs will be proposed for implementation later in the planning cycle.

A significant effort continues to be focussed on the analysis of data from the Collaborative Perinatal Project. Intensive studies are proceeding in the areas of febrile seizures, neonatal seizures, convulsive disorders in general, cerebral palsy, minimal brain dysfunction and maternal infection during pregnancy. Nichols (NDP) and Chen have completed a first draft manuscript of their book Minimal Brain Dysfunction. Nelson (NDP) and Ellenberg are at work on two books - one on the relationship of maternal variables and childhood signs to cerebral palsy, and the other, the association of these variables to seizures in children.

Pilot studies of clinical data banks have been initiated. The clinical data bank for stroke (Goals # 30,33,34) has been in operation for a year. During this time, a stroke vocabulary of some 450 variables has been developed along with data collection forms that will be used at each center and be regarded as part of the patient's medical record. The data forms are now being tested with actual patients from each of the participating centers, and it is expected that full-scale data collection will begin later this summer.

The medical centers that are participating in the clinical data bank for traumatic coma (Goals #36,37,38,40,41) have recently begun to collaborate on a number of aspects of the project, including the development of a coma vocabulary.

Data for a large number of stroke and trauma patients will be stored in the data banks and be available for research purposes.

The data can be analyzed using scientific methods for observational studies. It is anticipated that the data banks will lead to improved patient care through the investigation of important research issues.

Dambrosia, Ellenberg and Kunitz are producing a book Medical Data Bases: Construction and Research Considerations.

OBE is proceeding with an independent assessment of computer methodology used in data banks in order to develop specifications for a workable management system for databases in neurology.

Findings from the national surveys of neurological diseases are beginning to be disseminated. Several manuscripts on the clinical findings from the Stroke Survey (Goal #30) are in review for publication in the Journal Stroke as a supplement. A paper on the Stroke survey has been accepted for presentation at the 1979 ANA meeting. A brochure for a lay audience on the findings of the Stroke survey is in preparation.

A manuscript on the results of the Head and Spinal Cord Survey will be sent to the Journal of Neurosurgery for possible publication.

The initial effort of the contractor in the Brain Tumor Survey was determined to be less than adequate; the contractor subsequently developed and carried out a second phase of the research. A committee of survey statisticians is now considering ways of combining the two sets of data to provide single estimates.

In the Survey of Multiple Sclerosis all of the field work has been accomplished; hospitals, physicians, and a large sample of patients have been surveyed. By the end of this calendar year, estimates of incidence, prevalence and economic costs will be available. Future plans include a study of the validity of MS diagnoses among the survey respondents.

Planning and development are completed for the feasibility study for the National Hospital Survey of Disease, (Goal #30) a survey designed in collaboration with the National Center for Health Statistics, which will "piggyback" on the latter's Hospital Discharge Survey. Data collection will begin at 30 hospitals in early FY 1980.

The first phase of an investigation to determine the feasibility of a major survey of epilepsy (Goal #11) has been successfully completed. The results of this design test had been reviewed at a special meeting of the OBE Advisory Committee. The Committee recommended that OBE proceed to design the pilot study.

The field work in the Survey of Major Neurological Disorders (Goal #30) in Copiah County, Mississippi, has been completed.

The Bureau of the Census has completed the screening interviews of the residents of Copiah County, Mississippi, a community of 25,000 persons equally divided in the number of blacks and whites. Those found to be positive in the screen for senile dementia, stroke, psychomotor delay, epilepsy, Parkinsonism or cerebral palsy were examined by neurologists or pediatric neurologists on the staff of the University of Mississippi Medical Center. This survey is the first that will provide precise comparisons of the prevalence of these disorders between blacks and whites in a rural setting. The response rate for compliance with the screening interview was about 99 percent.

An epilepsy questionnaire was tested in the Mississippi Study for possible use in the NCHS Health Interview Survey.

Intramural Program research collaboration in biometry and mathematical statistics continues to be an important element of OBE activities with steadily increasing emphasis on full-scale collaboration of investigators in all phases of the projects. The range and variety of problems make full utilization of the varied talents of the OBE staff which, in addition to expertise in mathematical statistics, include those of physics and computer science; for example the latter two are heavily relied upon for the work in computer-aided tomography.

OBE has undertaken an intramural program of descriptive studies. A demographer has been added to our staff to conduct these studies and has begun several projects that will use data from the National Hospital Discharge Survey, the Health Interview Survey, the Health and Nutrition Examination Survey, and mortality records. These studies will aid OBE in becoming a source of statistical information for the Institute. Some of these studies will be limited to specific areas such as stroke and communicative disorders, while others will run the whole spectrum of disorders of interest to the Institute.

Planning for a National Headache Survey (Goals #55,57,58) is in progress. The objectives are: (1) to measure the extent of the problem of severe headache disorders in terms of incidence and prevalence, (2) to determine the impact of headaches on society and the headache population in terms of financial cost, work and productivity loss and quality of life, (3) to examine the use of medical-care services by the headache population, and (4) to identify etiological and environmental factors which may be associated with the occurrences of several major types of headaches. A draft of the medical section of the questionnaire has been developed and will be used to describe and identify several major types of headaches. Other sections in the questionnaire such as demography, impact and burdens, and the utilization of medical care services are under development by associates at the Johns Hopkins University.

A validation study of the medical and other sections of the questionnaire is being planned. There will be a review of clinical records of headache patients to develop an algorithm for identifying or classifying types of headaches and a series of interviews of headache patients to validate the classification system. A pilot study for testing and validating the survey instruments and methodology will be designed after completion of the initial phase of the work.

Another new initiative is the development of a three-stage program to determine the optimal management of children with febrile seizures (Goals #4,5,11,12). The first stage is a survey of current practice and of clinical determinants and rationale for management of children with febrile seizures. This will be used as an element in considering the need for and potential impact of further clinical research. The second is a consensus meeting on the management of children with febrile seizures. This mechanism would be used to determine if we currently have enough information for rational management of children with febrile seizures. Finally, a protocol for a clinical trial is under development in the event the results of the foregoing stages indicate such a trial is necessary and feasible.

The NDP Epilepsy Advisory Committee and the OBE Advisory Committee have recommended that NINCDS proceed with the three-stage program.

OBE is submitting the outline of a proposal for developing two colonies of aged monkeys, one in Bethesda, and the other in Puerto Rico, as a national resource for the study of senile dementia and the aging process in primates. (Goals # 17,19). These colonies can be organized rapidly from existing larger colonies, and descriptive studies could be published in FY'80. Cooperation of the Infectious Disease Branch, IRP, is assured, as is that of the Caribbean Primate Research Center, University of Puerto Rico. It is likely that the National Institute on Aging will offer to jointly fund the new program, given an invitation by NINCDS.

The National Institute on Aging has invited NINCDS to collaborate on a Survey of Senile Dementia and Other Mental Illnesses of the Aged (Goal # 17) which that Institute is jointly funding with NIMH. The survey will be a probability sample of individuals from the New Haven area and will include an oversample of persons aged 65 or over, so that some 2500-2600 elderly persons will be interviewed. The NIA has asked OBE to take responsibility for the analysis of the data of the sample of the elderly.

OBE is proceeding carefully with plans for organizing a Pain Clinical Data Base (Goals #55,57,58). Initial steps include the conduct of small workshops and studies of present efforts by individual university pain centers to establish pain data bases. OBE will be prepared to move forward with this project when the Stroke Clinical Data Bank Pilot Study has been completed and evaluated.

OFFICE OF BIOMETRY AND EPIDEMIOLOGY

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OFFICE OF BIOMETRY AND EPIDEMIOLOGY
Section on Mathematical Statistics

Consultation with IRP

- Dr. Yaar, Neuromuscular Section, Medical Neurology Branch: The effect of L-Dopa on EMG (electromyogram) measurements in human subjects.
- Dr. Pauline Chen, Laboratory of Perinatal Physiology: Brain tissue pressure in Hypoxic Kittens and Puppies.
- Dr. Hirsch, Laboratory of Perinatal Physiology: Study of hypercapnia and hypoxia in pregnant mice.
- Drs. Andrew Gal, Peter Pentchev, John Barranger, Roscoe Brady, Developmental and Metabolic Neurology Branch: The Distribution of Glucocerebroside in the Liver of Patients with Gaucher's Disease.
- Dr. Joanna Woyciechowska, Infectious Diseases Branch: Ragi cell protein aggregatum for the detection of M.S.
- Dr. Isabel Shekarchi, Infectious Diseases Branch: Determination of Rubella Antibody Levels using ELISA.
- Dr. R. Eldridge, Infectious Diseases Branch: Multiple Sclerosis and Household Pets.
- Rosemary Borke, Surgical Neurology Branch: Neuronal and Glial Response to Axone Injury in the Immature Rat.
- Sue Pollard and Dr. T. Chase, Intramural Research Program: Treatment with L-Dopa of PD Patients on Guam
- Dr. Richard J. Benfante, Laboratory of Central Nervous System Studies: Genetic Markers in Infection with Several Arboviruses.
- Dr. Paul Brown, Laboratory of Central Nervous System Studies: Creutzfeldt-Jakob Disease in France.
- Drs. Calne and Gopinathan, Experimental Therapeutics Branch: Treatment of Parkinson Patients with Lithium for Control of Dyskinesia.
- Drs. Calne and Gopinathan, Experimental Therapeutics Branch, LISURIDE Treatment of Parkinson Patients.
- Drs. Calne and Gopinathan, Experimental Therapeutics Branch, Tetrahydrobiopterine levels in Parkinson Patients.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

1. Univ. of Maryland (N01-NS-9-2302)
2. Univ. of S. Ala. (N01-NS-8-2397)
3. Duke Univ. (N01-NS-8-2396)
4. Boston Univ. (N01-NS-8-2398)

Title: PILOT DATA BANK NETWORK IN STROKE

Contractors' Principal Investigators:

1. Dr. Thomas Price
2. Dr. Jay Mohr
3. Dr. Albert Heyman
4. Dr. Philip Wolf

Current Annual Level:

1. \$ 95,705
2. 157,500
3. 104,876
4. 120,058

Objectives: The primary objective of this project is to develop a computerized interactive data bank network which will contain uniform, longitudinal data on stroke patients to aid both research and patient management. This is a collaborative project involving four separate medical centers which will collect data, a data base management center to store and manipulate the data, and staff at OBE who have the responsibility for data analysis.

Major Findings: This project has produced a uniform vocabulary of data to be collected on stroke patients from the collaborating centers. This vocabulary includes demographic background, diagnosis, signs, symptoms, test result, medical and surgical therapy, complications, and measures of stroke deficit and recovery. The methods and procedures for data collection and entry into the computerized data bank have been developed and are currently being tested at all centers.

Significance to the NINCDS Program and Biomedical Research: The Pilot Data Bank Network in Stroke is important for several reasons. First, the databank network will provide a resource of high quality data on the clinical course of stroke. It is intended that this data be used for research on the factors influencing stroke prognosis, and for other clinical investigations. Secondly, the interactive data bank provides the

physician with efficient data collection and timely access to patient data. Also projected is the provision of prognostic data from subgroups of similar patients. This is a pilot project, and is intended to serve as a prototype for a national databank network for neurological disorders.

Proposed Course of the Project: The Pilot Stroke Data Bank Network is completing a test phase (90 days) during which the uniform vocabulary, patient ascertainment procedures and data collection methods were being implemented on a trial basis. The data collected during this period will be extensively examined for errors. Any necessary revisions in methods or vocabulary will be made prior to the initiation of the actual data bank.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

RESEARCH TRIANGLE INSTITUTE (NO1-NS-8-2383)

Title: Test of Study Design and Pilot Study for a National Survey
of Epilepsy

Contractor's Project Director: Mr. Benjamin S. H. Harris, III

Current Annual Level: \$414,570

Objectives: This project was initiated to develop a new casefinding approach for ascertaining the incidence and prevalence of epilepsy. The previously used methods have serious deficiencies, and this proposal seeks to remedy them. The goal is to use pharmacies which fill prescriptions for anticonvulsive drugs, to lead to the physicians providing care and thus to the epileptics. By using techniques of probability sampling, estimates of the scope of the epilepsy problem could be obtained for the U. S. population.

Major Findings: The design test has been conducted by the Contractor and the proposal for the pilot study has been submitted to the Project Officer for approval.

Significance to the NINCDS Program and Biomedical Research: Morbidity surveys of relatively rare disorders are difficult to carry out for the U.S. population. One fundamental problem is that adequate numbers of cases for meaningful analyses may not be included in the sample of individuals selected for study due to stringent requirements for sampling a population. With epilepsy, the problem is compounded because of the perceived social stigma associated with having the disorder. The approach being tested in this contract will, if feasible, yield a cost-effective strategy for the sampling of epileptics who take anticonvulsive drugs. Furthermore, the privacy of the persons included in the study will be safeguarded to a great extent. If this strategy proves successful, a national survey of epileptics could be undertaken which would be invaluable to NINCDS and other organizations responsible for the planning of programs for epilepsy.

Proposed Course of the Project: The project is divided into two parts: a design test and a pilot study. The design test is on a very small-scale and its chief purpose is to lead to the development of methodology for data collection from pharmacies and physicians and to aid in the design of the pilot study. It is scheduled to be completed in July 1979. The pilot study is of a larger scale and its purpose is to resolve methodological issues which are raised by the investigators or are apparent after the design test. In addition, the pilot study will serve as a dry run for the procedures of the main survey. The pilot study will begin in fiscal year 1980.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

WESTAT, INC. (N01-NS-7-2379)

NATIONAL CENTER FOR HEALTH STATISTICS (Y01-NS-7-0030)

Title: National Hospital Survey of Disease
(formerly Comprehensive Disease Statistics Survey)

Contractor's Project Director: Westat, Inc. - Dr. Anita Schroeder
NCHS - Dr. Monroe Sirken

Current Annual Level: Contractor - \$250,000
NCHS - 59,400

Objectives: The objectives are to test the feasibility of obtaining hospital incidence and prevalence data for cases identified from abstracted hospital records of a number of neurological and other disorders, from a redesigned Hospital Discharge Survey of the NCHS. A key objective of a successful pilot study would be to develop a survey program that would permit the annual collection of data on these disorders in order to develop trends of their incidence and prevalence.

The national sample of short-stay hospitals would provide a stable base for special studies. These studies would include methodological problems such as multiplicity. It would also provide an unbiased sample of patients, for periodic studies of special interest such as costs of illness, degree of disability, duration of illness, etc. Comparability of data collection methods, and protocols from the same sample of short-stay hospitals, would also permit comparison across disease lines.

Major Findings: The study has been designed and the disease algorithms are being prepared. The contractor is now preparing detailed protocols for the feasibility study to be conducted in the fall of 1979 in 30 hospitals. NCHS has been involved in a cooperative effort with NINCDS to plan and design the study and to work on the many methodological and statistical problems involved in the survey.

Significance to the NINCDS Program and Biomedical Research: NINCDS has current contracts for surveys of four neurological disorders, and other surveys are underway and in the planning stage. For several reasons there is a need to consider a more comprehensive approach to the collection of disease statistics. First, there is a considerable degree of redundancy in the present approach, both within NINCDS, and, probably, across Institute boundaries. Redundancy leads to higher than necessary costs associated with the collection of disease statistics data. Second, the present approach leads to delays in obtaining current information, since there are a limited number of surveys which can be conducted at any one time. Third, the methods and protocols used by each contractor differ, and this affects the comparability of data across disease lines. Fourth, and perhaps most important, these data provide planning information based on a limited time period, when in fact

trend data, obtained on an annual, prospective basis, would better serve the program planning and program evaluation functions.

The development of a comprehensive system for the collection of disease statistics on a wide variety of diseases would be of great value to NINCDS and other NIH Institutes for it would eliminate the four above-mentioned major problems.

This proposal would establish a cooperative and joint relationship between NCHS and NINCDS, and would provide for an NCHS collection of national health statistics of considerable interest to NINCDS, and potentially, to other NIH Institutes. It would, to the extent that incidence and prevalence data can be obtained from records at short-stay hospitals, supplant NINCDS data collection efforts. NINCDS would continue to analyze the data collected to meet its own program planning needs.

Proposed Course of the Project: This project is a joint venture. The contractor will be responsible for only part of the study. The contractor will develop the methodology and protocols for the feasibility study and the pilot study, will provide the field staff, and will conduct the study and process the data. The disease algorithms will be prepared by NINCDS staff with the aid of other participating NIH Institutes. The sampling plan, counting rules for non-duplication of cases, estimation of sampling variances, and coordination with participating hospitals will be conducted by the National Center for Health Statistics, HRA, under a separate interagency agreement.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

WESTAT, INC. (N01-NS-6-2333)

Title: Nationwide Study of Stroke

Contractor's Project Director: Morton Robins

Current Annual Level: \$7,677

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of stroke. It would be accomplished by devising and testing a method for carrying out the survey, and for presenting the statistical results of the survey, including the sampling errors.

Major Findings: The field work of the survey and the data analyses have been completed. A clinical algorithm was applied to the abstracted hospital records which classified the records according to type of stroke and degree of confirmation of the diagnosis in the medical records. Analyses have been made relating the clinical data with the type of stroke and selected age-sex groupings. The final report has been received from the contractor. This report has been reviewed and a series of articles containing the clinical, epidemiologic, and economic findings are being written for submission for publication in a professional medical journal or as a supplement to the journal.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of stroke. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The medical records were abstracted and pertinent information on the patient's demographic characteristics, the diagnostic categorizations of the stroke, date of onset, medical history of previous strokes or TIA's, clinical signs and symptoms, diagnostic findings, treatment, and outcome of hospital care were recorded for each stroke discharge selected in the sample hospitals. In addition, the hospital's business office was asked to furnish data on the direct medical charges to the patient or third party payer on those cases discharged during 1975. A subgroup of surviving patients (or close relatives) was also interviewed to obtain information on direct expenditures related to the stroke incurred

during 1975 by the patient or the family. Additional facts on other aspects of economic impact of a stroke on the patient and the family were collected. Moreover, for those discharged patients in the sample that were presumed to have had an initial stroke attack, their survival status was determined as of December 31, 1975, in order to calculate prevalence. The data collected in this survey has been analysed and the final report from the contractor has been received. This contract is now completed. The final report has been reviewed and a series of articles containing the clinical, epidemiologic, and economic findings are being written for submission to a professional medical journal. A monograph of the complete study will also be published in fiscal year 1980.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

NATIONAL ANALYSTS, INC. (N01-NS-4-2335)

Title: Survey of the Incidence, Prevalence, and Costs of Multiple Sclerosis

Contractor's Project Director: Beth Rothschild

Current Annual Level: \$200,000

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of multiple sclerosis.

Major Findings: The first and nearly all of the second phase of the study have been completed. The data on providers (physicians and hospitals) has been processed. All the patient logs--containing 90-day expense and activity histories--and the closing telephone interviews have been collected. The first patient data tape has been completed. In fiscal year 1980 the data will be analyzed and a report of the findings will be prepared.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of multiple sclerosis. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in health research. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: In the fiscal year 1980 the contractor will: edit and complete the patient cost data tapes; develop incidence and prevalence estimates for the various patient groups; analyze the cost data; perform various other analyses based on all the different types of data collected; prepare a final report; and prepare three journal articles on the results of the study.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

UNITED STATES BUREAU OF THE CENSUS (Y01-NS-7-0031)
UNIVERSITY OF MISSISSIPPI (N01-NS-7-2357)

Title: Survey of Major Neurological Disorders in Copiah
County Mississippi

Contractor's Project Director: Mr. Robert W. Mangold (Bureau
of the Census); Dr. Armin F. Haerer (University of Mississippi)

Current Annual Level: \$200,000 (Bureau of the Census);
\$ 5,000 (University of Mississippi)

Objectives: The primary objective of the proposal is to establish the prevalence of six major neurological and developmental disorders (cerebrovascular disease, convulsive disorders, cerebral palsy, psychomotor delay, Parkinson's disease, and dementia) in a well-defined population of southern blacks and whites. A secondary objective is to evaluate the sensitivity and specificity of certain screening questions by means of an item analysis at the close of the study. This analysis is needed because effective screening questions will be used in other morbidity surveys (e.g., the Health Interview Survey of NCHS).

Major Findings: The data collection phase has been completed. The data processing phase is ongoing and strategies are being developed for the data analysis.

Significance to the NINCDS Program and Biomedical Research: At present, there are no adequate data on the prevalence of the six disorders of interest among southern blacks and whites in the United States. A number of studies suggest that stroke is more common among the black population. Mortality data and a few morbidity studies suggest that Parkinson's disease is less common among blacks. A biological explanation of this observation is that both melanin and dopamine are involved in the same metabolic pathway. Dopamine-deficiency in the basal ganglia has been found in patients with Parkinson's disease and is the rationale for the treatment of this condition with L-dopa. Blacks have a higher concentration of dopamine in the basal ganglia than whites which could explain a lower frequency of Parkinson's disease. On the other hand, it may be that blacks with this condition do not seek medical care or receive inadequate care. Mortality tabulations, with all of their biases, suggest that blacks have a predominance of epilepsy and cerebral palsy, but this requires confirmation with morbidity data. The magnitude of the dementia problem has not been studied in any United States population and Copiah County will provide some indication as to whether there is a racial and sex differential in the frequency of this group of conditions.

Proposed course of the project: The field operations for the main study were divided into two types of operations. The first was a household screening operation which was conducted by the Bureau of the Census. Residents of the study area were screened in their homes by means of a questionnaire administered by lay interviewers who were trained and supervised by the Bureau of the Census. The second type of operation was the examination of persons suspected of having one or more of the disorders of interest on the basis of responses given to questions from the screening questionnaire. The University of Mississippi provided senior, board-certified neurologists to accomplish the neurological examinations and to record the medical findings on forms designed especially for this study. After the close of the field operations, the data was sent to the Bureau of the Census for processing. When the data tapes and files are available for analysis, the Project Director and Associate Project Director from the University of Mississippi will assist NINCDS in the data analysis and the preparation of scientific papers based on the findings of the survey.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

RESEARCH TRIANGLE INSTITUTE (N01-NS-4-2334)

Title: Survey of the Incidence, Prevalence and Costs of
Head and Spinal Cord Injury

Contractor's Project Director: Dr. Daniel G. Horvitz

Current Annual Level: No cost to the Government

Objectives: The chief aim of the NINCDS National Head and Spinal Cord Injury Survey was to develop estimates of incidence, prevalence, and economic costs for the United States population and selected subpopulations. These estimates were based on a sample of cases which have been selected using the techniques of probability sampling. These techniques are generally more expensive to use than other techniques of sampling but they offer the only general approach which permits the determination of levels of precision for the sample estimates. In this NINCDS survey, levels of precision were obtained for the major estimates of interest.

Major Findings: The objectives of this survey have been realized and the findings have been presented to NINCDS in the form of a final report. NINCDS staff have reviewed the final report and are now preparing a manuscript on substantive findings which will be published as a supplement to a major journal.

Significance to the NINCDS Program and Biomedical Research: The Head and Spinal Cord Injury Survey of NINCDS will have major impact on Institute programs in two distinct ways. First, the survey was designed as a tool for program planning. It provides an indication of the scope of the head and spinal cord injury problem as well as the economic costs (both direct and indirect costs) of the problem. With this information, and information from surveys of other disorders, program planners are better able to justify their research priorities and needs.

Second, this survey and others sponsored by NINCDS established that national surveys of relatively rare disorders can be feasible in certain instances using a case finding approach. This realization led to the development of a multipurpose survey which encompasses many disorders. The multipurpose survey will be a periodic survey in which estimates pertaining to various points in time (e.g., yearly, every five years) are obtained and analyzed for trends. This multipurpose survey will be major in scope and will have a significant impact on the programs of several NIH Institutes, the National Center for Health Statistics, and the Center for Disease Control.

Proposed Course of the Project: The study is completed and the final report has been submitted.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

Stanford Univ. (N01-NS-8-2390)

Title: Data Bank Maintenance Center for Pilot Data Bank
Network Projects in Stroke and Traumatic Coma.

Contractor's Project Director: Dr. James F. Fries

Current Annual Level: \$147,856

Objectives: TOD-ARAMIS is the Data Bank Maintenance Contractor for the Pilot Projects to establish Data Bank Networks for Stroke and Traumatic Coma. During the three and a half year contract period ARAMIS will provide the computer interface for these projects, which includes data entry, storage, and retrieval, utilizing the Time-Oriented Data Base (TOD) system. Data will be collected at pilot centers and entered into separately maintained Stroke and Coma data banks available for retrieval within and among the pilot centers.

Major Findings: TOD-ARAMIS has created the computer Schema for the Stroke Data Bank uniform vocabulary and developed the methods for entering the Stroke data into the central data bank. The Schema is a dictionary of data elements contained in the patient chart. Data entry personnel at the four stroke centers have been trained and some retrieval programs have also been developed.

Significance to the NINCDS Program and Biomedical Research:
The TOD-ARAMIS Data Bank Maintenance Center is crucial to the success of the eight data banks which comprise the Pilot Data Bank Networks for Stroke and Traumatic Coma. TOD-ARAMIS serves as the central data repository, maintains data integrity and provides programming, education, and systems support to the eight centers. The availability of this database computer software has made these data bank networks feasible without extensive investment in new programming activity; applying this system to stroke and traumatic coma is a first step in the development of an optimal system for a national data bank network for neurological disorders.

Proposed Course of Project The Stroke schema is complete and the present focus is on data entry during the current test phase of the Pilot Stroke Data Bank Network. By the early part of FY 1980 the test phase will end and the Maintenance Center will focus its activities on storage and retrieval for Stroke. The recently awarded Coma data bank contractors are still developing their vocabulary; when it has been completed, TOD-ARAMIS will construct the Coma schema.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

RESEARCH TRIANGLE INSTITUTE (263-78-C-0132)

Title: Case Verification and Supplemental HSCI Analyses

Contractor's Project Director: Mr. Paul Moore

Current Annual Level: \$ 7,725

Objectives: After careful examination of the final report of the Head and Spinal Cord Injury Survey (Contract N01-NS-4-2334), it became evident that not all needed analyses had been anticipated and carried out prior to the expiration of the contract. The primary objective of this project is to undertake new analyses which will enhance the value of the monograph to be published on major findings from the survey. In addition, the algorithm which has been used in the main survey to determine medical eligibility for cases of spinal cord injury is to be evaluated in a small-scale specificity investigation.

Major Findings: NINCDS has received the new analyses and a report on the validity check.

Significance to the NINCDS Program and Biomedical Research: This project is of critical importance to NINCDS because the findings are needed for the major report on the Head and Spinal Cord Survey which will be published in a prestigious medical journal. The report will likely have a significant impact on the health care providers who have an interest in injuries to the head and spinal cord.

Proposed Course of the Project: This contract was of short duration and the objectives have been reached.

CONTRACT NARRATIVE
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

WESTAT, INC. (N01-NS-4-2336)

Title: Survey of Intracranial Neoplasms

Contractor's Project Director: Thomas G. McKenna

Current Annual Level: \$53,000

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of intracranial neoplasms.

Major Findings: The main survey has been completed and the findings have been presented to NINCDS by the contractor in the form of a final report. The report has been reviewed and additional data is being collected from the hospitals and certain analyses are being redone to improve the quality of the findings. The clinical, epidemiologic and economic findings will be presented in articles which will be submitted for publication in a professional medical journal.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of intracranial neoplasms. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The main study has been completed and the final report was submitted by the contractor. After careful examination of the final report it became evident that certain ICDA categories needed to be examined in order to validate the findings before publication. Some of the participating hospitals have been asked to furnish photocopies of selected patient records and the data will be reanalysed. The contract has been extended in order to complete the study. The clinical, epidemiologic and economic findings will be presented in articles which will be submitted for publication in a professional medical journal.

Contract Narrative
Office of Biometry and Epidemiology, OD, NINCDS
Fiscal Year 1979

1. Univ. of Texas-Galveston (N01-NS-9-2308)
2. Univ. of Cal. in La Jolla (N01-NS-9-2309)
3. Medical College of VA (N01-NS-9-2307)
4. Univ. of VA (N01-NS-9-2306)

Title: Pilot Data Bank Network in Traumatic Coma

Contractors' Principal Investigators:

1. Dr. Robert Grossman
2. Dr. Lawrence Marshall
3. Dr. James D. Miller
4. Dr. John Jane

Current Annual Level FY79

1. \$ 99,787
2. 116,638
3. 123,559
4. 97,246

Objectives: The primary objective of this project is to develop an interactive data bank network for traumatic coma patients. This databank will be used for clinical research and patient management.

Major Finding: These contracts have recently been awarded and the investigators have met once to discuss the uniform vocabulary and data collection methods. This databank will refine and utilize a uniform clinical vocabulary to collect patient data, including symptoms, test results, therapies and outcomes. The Glasgow Coma Scale will be part of this vocabulary. Sections of the vocabulary were selected for revision and assigned to each of the investigators.

Significance to the NINCDS Program and Biomedical Research:
This Traumatic Coma Data Bank is important for several reasons. Longitudinal data on coma victims will be collected at four centers using uniform definitions and procedures. This information will provide a large body of high quality data for clinical research on the factors influencing survival following coma. Secondly, the databank will serve as an efficient mechanism for collecting, storing, and retrieving the information collected on a single patient and groups of patients. The number of therapies and monitoring devices commonly utilized

during the acute phase of managing traumatic coma necessitates a highly organized data handling capacity. The preliminary utility of this databank network for clinical research and patient management will be demonstrated.

Proposed Course of the Project: This is a three year collaborative pilot project involving four centers which will collect patient data, a database management center, and OBE staff which will provide some systems support and have the responsibility for data analysis. During the first stage of its operation the effort is being focused on refining the uniform vocabulary and developing data collection methods. The second stage will be a test phase when this vocabulary and procedures for collection, entry and retrieval are implemented on a trial basis. Later stages will involve final revision of vocabulary and methods, implementation and analysis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02310-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) A Statistical Study of Sensory-Decision-Theory Method in the Measurement of Experimental Pain		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Office of the Chief		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is to study the <u>Sensory-Decision-Theory Method</u> in determining sensory discriminability and response bias in experimental pain. The investigation of the <u>parametric approach</u> for the evaluation of pain response components, d' and β (as proposed by Clark, 1971) has been completed. The result of this study has been reported at the Second World Congress on Pain 1978. Current work involves investigation of the <u>nonparametric</u> estimation of the indices of pain response components (Pollack 1964, Hodos 1971, McNicol 1972). The sampling behavior of these indices will be extensively studied.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02342-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Association of Multiple Sclerosis with Certain Serological Parameters.		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBE, NINCDS		
COOPERATING UNITS (if any) George W. Ellison, M.D., Associate Professor, Reed Neurological Center, UCLA		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Office of the Chief		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.1	PROFESSIONAL: 0.1	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this study is to investigate whether different <u>types of multiple sclerosis</u> (as defined by Reed Neurological Center, UCLA) are associated with <u>levels of certain serological measurements</u> such as IgG, IgM, Measles and EBV titers. Statistical analysis of clinical data indicated that multiple sclerosis patients of different types (relapse, relapse-progressive, progressive) differed significantly from control patients in certain serological parameters. Current work involves analysis of additional clinical data and preparation of a study report.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02404 - 01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) National Headache Survey		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Robert Baumann, M.D., Neurologist, OBE, NINCDS PI: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBE, NINCDS PI: Frederic D. Weinfeld, Ed.D., Chief, Section on Surveys and Demographic Studies, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Office of the Chief, and the Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is to measure the extent of the problem of chronic, severe and disabling headaches, the impact of headache disorders on society, and the headache population. In addition, it is planned to examine the present usage of health care by the headache population and to identify etiological and environmental factors which may be associated with various types of headache. The survey questionnaire which includes sections on demography, medical information and history, cost, work and financial loss, etc., is currently under development. A validation study of the questionnaire and the algorithm for identification of major types of headaches are also being designed.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02312-03 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Methodology for Systematic Statistical Analysis of Multiple Antibody Readings on Matched Controlled Studies.		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Alan J. Talbert, Statistician, Section on Mathematical Statistics, OBE, NINCDS Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS Other: John L. Sever, Chief, Infectious Diseases Branch, NINCDS		
COOPERATING UNITS (if any) Infectious Diseases Branch, NINCDS		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Mathematical Statistics, OBE, OD, NINCDS		
INSTITUTE AND LOCATION NIH, NINCDS, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A system was developed for analysis of <u>multiple antibody response data</u> in paired sera from <u>matched control studies</u> . The system includes an exacting data quality control step and comprehensive statistical testing to compare abnormals with controls, and to detect and flag seroconversions. The serology analysis system has been extensively updated, including improvements in chi-square tests with low expected cell frequencies and in Kolmogorov-Smirnov tests when sample size is small. Ease of use, output displays, and documentation have been improved and updated.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02347-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Observational Study of a Clinic Population of Cerebral Palsy Patients		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Leon Root, Director of CP Clinic, Hospital for Special Surgery, NYC, NY P.I.: Robert Richter, Mathematician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Hospital for Special Surgery, N.Y.C Cerebral Palsy Clinic, Leon Root, Director		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .25	PROFESSIONAL: .25	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project is an observational study of a large urban clinic population of <u>cerebral palsy patients</u> . The population to be examined consists of approximately 1,000 Cerebral Palsy patients of the Hospital for Special Surgery in New York City. Staff of OBE collaborated on the definition of the standardized vocabulary, designed the data collection protocols and established a quality control mechanism for data collection. The results of the initial pilot phase for data collection necessitated major revisions in the data collection protocol with a greater emphasis in the surgical area. A <u>second data collection</u> pilot is in progress.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02350-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Statistical Methodology for Medical Data Bases		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: James M. Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBE, NINCDS Other: Selma Kunitz, Head, Section on Systems Design and Data Processing, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .3	PROFESSIONAL: .3	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Data bases for stroke and traumatic coma provide observational data that require both critical application of existing <u>statistical methodology</u> and development of <u>new statistical techniques</u> , in order to extract meaningful information and to draw valid conclusions from the accumulated data. Methodology has been developed to ensure validity and quality control of the collected data. Methods for data analysis which take account of variation due to observers, centers, and patient cohort characteristics are being developed. An invited paper concerning the use of medical data bases for clinical research was presented at the Annual Eastern Regional Biometrics Society Meeting in April 1979.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02351-02 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (90 characters or less) Improving Current Methods of Analyzing Molecular Hybridization Experiments		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Rosalind B. Marimont, Research Mathematician, Section on Mathematical Statistics, OBE, NINCDS PI: Lawrence D. Grouse, Medical Officer, Laboratory of Developmental Neurobiology, NICHD		
COOPERATING UNITS (if any) Laboratory of Developmental Neurobiology, NICHD		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .2	PROFESSIONAL: .2	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Many <u>hybridization</u> experiments are analyzed by fitting the time curve of percent of <u>DNA</u> or <u>RNA</u> hybridized to various forms of the second order rate equation. Empirical correction factors must be applied for proper interpretation of results. Since the precise assumptions on which this method of analysis are based have not always been made clear, there is some uncertainty about applicability of particular equations. Also some laboratories lack sufficiently <u>general curve fitting programs</u> . The computer system MLAB, available at NIH and some other installations, has been recommended for its power and generally in curve fitting and model building. One simple but important question -- under what ranges of <u>initial tracer to driver concentration</u> are two of the commonly used <u>approximations to the second order rate equation</u> valid -- has been answered by computing and displaying the appropriate curves over a large range of initial concentrations. A paper has been prepared.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02352-02 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Nearest Neighbor Algorithms for High Dimensional Spaces		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Rosalind B. Marimont, Research Mathematician, Section on Mathematical Statistics, OBE, NINCDS PI: Marvin B. Shapiro, Mathematician, Laboratory of Statistical and Mathematical Methodology, DCRT		
COOPERATING UNITS (if any) Laboratory of Statistical and Mathematical Methodology, DCRT		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .4	PROFESSIONAL: .4	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <p> The geometric <u>nearest neighbor problem</u> is to choose from a fixed collection of points (the library) in a 'd' dimensional space that point nearest to a given query point. Many <u>classification</u> and <u>pattern recognition</u> problems are exact analogues of the geometric problem if coordinates and distance measure are suitably defined. Most <u>cutoff algorithms</u> effective in low dimensional spaces deteriorate for $d > 10$. Analysis of these algorithms in terms of mapping from a high to low dimensional space shows that if the mapping function and image space are suitably chosen, cutoff algorithms can be effective at higher dimensionality. It is shown that in most cases, the image space must be of dimension approximately $d/2$, and that principal components analysis can be used to optimize the choice of the image space. Results were published in the <u>Journal for the Institute of Mathematics and its Applications</u>. </p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02353-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Synthesis of Graph and Matrix Theory		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Rosalind B. Marimont, Research Mathematician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .2	PROFESSIONAL: .2	OTHER: 0
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 30%;"> <input type="checkbox"/> (a) HUMAN SUBJECTS </div> <div style="width: 30%;"> <input type="checkbox"/> (b) HUMAN TISSUES </div> <div style="width: 30%;"> <input checked="" type="checkbox"/> (c) NEITHER </div> </div> <div style="display: flex; justify-content: space-between; align-items: flex-start; margin-top: 5px;"> <div style="width: 30%;"> <input type="checkbox"/> (a1) MINORS </div> <div style="width: 30%;"> <input type="checkbox"/> (a2) INTERVIEWS </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) This is a long-term effort to combine the concepts and methodology of <u>graph theory</u> and <u>matrix theory</u> to facilitate understanding of and solution of a large class of problems for example, <u>linear compartmental systems</u> . A previous matrix-graph theorem was extended. A <u>series</u> important in statistics was summed and its general behavior described by deriving its <u>recursive form</u> through graph-matrix methods. Several other series were also shown to be expressible in recursive form, which greatly simplifies their computaton.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02354-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Clinical Trial of Efficacy of Phenobarbital as Prophylaxis for Children with Febrile Seizures		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS P.I.: Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS		
COOPERATING UNITS (if any) Cerebral Palsy and Other Motor Disorders Section, Developmental Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Six percent of all <u>children with febrile seizures</u> are at relatively high risk for later afebrile activity. A proposal is being devel- oped for a <u>clinical trial</u> which will examine the efficacy and tox- icity of chronic and short-term prophylaxis with phenobarbital for this group of children. At present chronic prophylactic medication is recommended by several authors without available information as to the potential success or side effects of such medication.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02409-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Image Reconstruction Theory		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS P.I.: Alan J. Talbert, Statistician, OBE, NINCDS		
COOPERATING UNITS (if any) Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Computer simulations of CT scans have been made in the development of an improved method of back projection in Computed Tomography. This method employs interpolation in both the ρ and ϕ polar coordinates.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02410-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Dual Energy Scanning		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS P.I.: Alan J. Talbert, Statistician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Methodology has been implemented for optimizing the use of dual energy x-ray scans to obtain information on chemical constituents of scan subjects. Two papers on this work have been accepted for publication and a third paper is in preparation.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02411-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Survey of Management of Children with Febrile Seizures		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS P.I.: Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS		
COOPERATING UNITS (if any) Cerebral Palsy and Other Motor Disorders Section, Developmental Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .2	PROFESSIONAL: .1	OTHER: .1
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) As a first step in considering an expensive and prolonged clinical trial of prophylactic treatment for febrile seizures, a survey of clinical practice is being designed, to determine which medical discipline/s treat most children with febrile seizures, what criteria physicians employ to determine therapy, the regimens prescribed, and the specific goals of therapy. The resultant information will be used in determining the parameters of any future clinical trial.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02412-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Consensus Meeting on the Management of Children with Febrile Seizures		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS P.I.: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Cerebral Palsy and Other Motor Disorders Section, Developmental Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .2	PROFESSIONAL: .1	OTHER: .1
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINDRS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Febrile seizures in young children are very common, affecting 3-4% of the pediatric population, yet there is still no consensus as to their optimal medical management. The possible consequences of febrile seizures, including their effect upon later physical and intellectual development and upon the likelihood of later chronic epilepsies, have been uncertain on the basis of available medical information. Since the use of chronic anticonvulsant medication may not be without risk in the very young child, it is necessary, in considering the need for treatment, to evaluate the risks in the natural history of the disorder. The next reasonable step is to consider the risks and benefits of chronic prophylaxis. The purpose of the consensus meeting is the reassessment of the available evidence in an effort to reach a rational policy of clinical management as guidance to the practicing community.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02413-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Study of Lithium to Control Dyskinesia in Levadopa-Treated Parkinson Patients		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: D. Calne, Chief, Experimental Therapeutics Branch, IRP, NINCDS Others: R. Giopinathan, Therapeutics Section, Experimental Therapeutics Branch, IRP, NINCDS James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Therapeutics Section, Experimental Therapeutics Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A study was undertaken to determine the feasibility of conducting <u>a randomized controlled clinical trial of lithium for the reduction</u> <u>and control of levadopa induced dyskinesia in Parkinson patients.</u> The major problem area is the clinical measurement of dyskinesia and the associated lithium response. A number of quantitative measurement methods are presently being investigated for use in the proposed study. If the trial is undertaken a two period crossover design will be used with a nonparametric analysis of the data.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02414-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Simulation of Early Stopping Rules Used in Clinical Trials		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBE, NINCDS P.I.: Jonas Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) In clinical trials with a specified survival time as the stated endpoint, a number of ad hoc statistical procedures have been proposed as guides to early trial termination. Distribution theory for these statistics is either mathematically intractable or only known asymptotically. A computer simulation study for comparison of the various procedures is being conducted.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02415-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Cage Standards for Primates		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Amos Palmer, Research Veterinarian, Infectious Diseases Branch, IRP, NINCDS Other: James Dambrosia, Mathematical Statistics, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Infectious Diseases Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .05	OTHER: .05
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Present cage assignments for primates is based solely on the animal's weight. Variation in shape between species of primates of the same weight indicate that the current weight based standard may be inappropriate. A large number (410) primates of 4 different species have been measured (arms, legs, chest, tail, crown to rump, crown to heel) in order to determine association of and variations in weight as functions of shape measurements.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02416-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Gantry Motion Study for a Positron Scanner		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS P.I.: Alan J. Talbert, Statistician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) By means of computer simulations a nearly optimum gantry wobble scheme has been discovered for use in the design of a positron scanner being built at NIH. A paper has been published on this subject.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02417-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Doubly Linked List Processing Algorithm		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Alan J. Talbert, Statistician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) An algorithm was devised to process a doubly linked list by computer. Such lists are useful in applications requiring insertion and deletion of list items at arbitrary positions in a list sorted by ascending keys. Processing is simpler than for trees and is preferable for small lists. This capability facilitated computations of overlapping session times in a survey of computer terminal usage.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02418-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Elective Hysterectomy and Antibiotics		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Robert Richter, Mathematician, Section on Mathematical Statistics, OBE, NINCDS P.I.: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS P.I.: John H. Grossman III, Assistant Professor, OBS-GYN, Guest Worker, Infectious Diseases Branch, NINCDS		
COOPERATING UNITS (if any) George Washington Medical Center, OBS-GYN Infectious Diseases Branch, IRP		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project involves the study of the effects of antibiotics on bacterial infections in 100 women undergoing elective hysterectomy in the Yale-New Haven Hospital from 1973 to 1977. Antibiotics used were Penicillin and Cefazolin. Staff members of OBE are collaborating on the extensive data analysis, including multivariate analysis of variance for categorical data.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02419-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Cost Considerations in the Generation of Large Correlation Matrices		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Robert Richter, Mathematician, Section on Mathematical Statistics, OBE, NINCDS PI: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS PI: Daniel Chambers, Mathematical Statistician, Department of Mathematics, University of Maryland		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The evaluation of cost differentials in the use of SPSS, BMDP and PSTAT statistical packages to generate large (120x120) correlation matrices was completed using NIH's computer system. The results of this work have been used to select the least expensive statistical package for use with the analysis of the Collaborative Perinatal Project. This material has been submitted for publication.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02420-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Minicomputer Acquisition		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Robert Richter, Mathematician, Section on Mathematical Statistics, OBE, OD, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .20	PROFESSIONAL: .20	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project involved the procurement of a HP-1000 minicomputer. An OBE staff member collected and analyzed statistical and graphics requirements from each OBE section and translated these needs into hardware and software requirements. An intensive search of commercial and governmental resources (including NIH's) yielded three sources IBM, Digital Equipment Company and Hewlett Packard (HP) that met most requirements. The HP-1000 minicomputer was selected and an initial configuration was designed, purchased and delivered.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02421-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Assessment of Robustness of Missing Data Techniques		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBE, NINCDS P.I.: Daniel Chambers, Mathematical Statistician, Department of Mathematics, University of Maryland		
COOPERATING UNITS (if any)		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .25	PROFESSIONAL: .15	OTHER: .1
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Several techniques for handling missing observations in the statistical analysis of large data sets have been proposed. All of the existing techniques require certain assumptions about the underlying model; generally this includes the assumption that the missing data are randomly generated and randomly dispersed within the data set. This project is assessing the robustness of the standard techniques to variations in the underlying assumptions, such as nonrandomness and high intercorrelations within the data set. The project will be accomplished using computer simulation on our HP-1000 mini computer.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02422-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Aliasing Errors in Computed Tomography		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS P.I.: Alan J. Talbert, Statistician, Section on Mathematical Statistics, OBE, NINCDS		
COOPERATING UNITS (if any) Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS		
LAB/BRANCH Biometry and Epidemiology		
SECTION Mathematical Statistics		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Computer simulations of computed tomography scans were made in conjunction with theoretical work for the purpose of obtaining a better understanding of aliasing errors in CT and of evalua- ting several remedies for these errors. A paper has been pub- lished on this work.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02407-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Assessment of Databank Methodology		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Selma C. Kunitz, Head of Section on Systems Design and Data Processing, OBE, OD, NINCDS Other: Sylvia Edelstein, Chief Programmer, SSD, DP, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Systems Design and Data Processing, OBE, OD, NINCDS		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .7	PROFESSIONAL: .5	OTHER: .2
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A project to <u>assess</u> the computer methodology used in the Pilot Data Bank networks in Stroke and Traumatic Coma is proposed. Its purpose is to 1) compare the methodology (hardware and software) in these pilots to other available <u>data base management systems</u> , 2) develop specifications for modifying or replacing all or part of the current system, (TOD), in order to obtain a more optimal system, and 3) if appropriate, implementation of the specifications for an optimal data base management system for a <u>National Databank for Neurologic Disorders</u> .		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02408-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Clinical Databanks As a Resource for Epidemiologic Research		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Cynthia Gross, Ph.D. Biostatistician-Epidemiologist SSD & DP, OBE, OD, NINCDS Other: Selma C. Kunitz, Head, Section on Systems Design and Data Processing, OBE, OD, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Systems Design and Data Processing, OBE, OD, NINCDS		
INSTITUTE AND LOCATION NIH, NINCDS, Bethesda, Maryland 20205		
TOTAL MANYEARS: .3	PROFESSIONAL: .3	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Much has been written on the use of observational studies in <u>epidemiological research</u> . It will be necessary to apply many of the same epidemiologic techniques used in conventional observational studies to the <u>clinical data bank</u> . Work on determining which epidemiologic approaches are most appropriate for use with clinical data banks has begun in conjunction with the Stroke and Traumatic Coma Databank Networks (N01-NS-8-2396, 78, N01-NS-9-2302, 6, 7, 8, 9).		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02341-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Type-Specific Stroke Mortality Trends (Previously titled: "Stroke Mortality Study")		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Herbert M. Baum, Ph.D., Survey Statistician, OBE, NINCDS PI: Frederic D. Weinfeld, Ed.D., Head, Section on Surveys and Demographic Studies, OBE, NINCDS Others: Bernard H. Kroll, Associate Chief, OBE, NINCDS		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .30	PROFESSIONAL: .25	OTHER: .05
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) There is a need to examine stroke mortality trends by specific types of strokes. OBE has obtained the mortality data tapes for 1968-1976, and will use these tapes to examine age-type specific stroke trends by race and sex. There are many problems inherent in such a study, but the results would be useful to health planners and administrators. Additionally, this study will be useful in generating hypotheses OBE may be interested in examining at a later date.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02401-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) The Relationship Between Stroke and Speech and Hearing Defects		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Herbert M. Baum, Ph.D., Survey Statistician, OBE, NINCDS PI: Christy L. Ludlow, Ph.D., Research Speech Pathologist, Communicative Disorders Program, NINCDS		
COOPERATING UNITS (if any) Communicative Disorders Program, NINCDS		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .10	PROFESSIONAL: .08	OTHER: .02
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The 1977 <u>Health Interview Survey</u> had supplements on <u>hearing</u> and <u>stroke</u> . The data on these disorders are to be analyzed in conjunction with what is regularly collected about <u>speech</u> defects. The analysis will yield estimates on the complications resulting from stroke and we will examine whether these complications can be used as an indicator for stroke in interview surveys.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02402-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) An Examination of Speech and Hearing Problems as Detected in HANES II		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Christy L. Ludlow, Ph.D., Research Speech Pathologist, Communicative Disorders Program, NINCDS PI: Herbert M. Baum, Ph.D., Survey Statistician, Section on Surveys and Demographic Studies, OBE, NINCDS		
COOPERATING UNITS (if any) Communicative Disorders Program, NINCDS		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .05	PROFESSIONAL: .04	OTHER: .01
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The Communicative Disorders Program anticipates conducting a survey of <u>speech disorders</u> among 2-6 year olds. Current work is focusing on constructing a valid test instrument. Concurrently, our Office is assisting in examining similar work done by the <u>HANES II</u> . We intend to use the experience and results from the HANES to determine the feasibility of the survey and what problems should be avoided. We are also exploring the possibility of conducting the survey as part of a future phase of the HANES.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02403-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) The Incidence and Prevalence of Stroke		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Frederic D. Weinfeld, Ed.D., Head, Section on Surveys and Demographic Studies, OBE, NINCDS PI: Herbert M. Baum, Ph.D., Survey Statistician, OBE, NINCDS		
COOPERATING UNITS (if any) Morton Robins, Project Director, Nationwide Study of Stroke, Westat Inc., Rockville, Md.		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .50	PROFESSIONAL: .25	OTHER: .25
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Estimates of the <u>incidence</u> and <u>prevalence</u> of <u>stroke</u> were generated from the findings of the <u>National Study of Stroke</u> . These are being prepared for publication as a journal article, and for comparison with other commonly accepted estimates of incidence and prevalence.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02405-01 OBE
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Assessment of Strategies for Analyzing Data From Small Area Mortality Surveys		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Dallas W. Anderson, Ph.D., Section on Surveys and Demographic Studies, OBE, NINCDS		
COOPERATING UNITS (if any) W. Edwards Deming, Ph.D., Consultant in Statistical Studies, Washington, D.C.		
LAB/BRANCH Office of Biometry and Epidemiology, OD, NINCDS		
SECTION Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .10	PROFESSIONAL: .09	OTHER: .01
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Studies of small areas, such as communities or counties, are an important tool of <u>epidemiologists</u> , who are interested in studying the distribution of particular diseases in populations. Many studies of this type have been reported in the scientific literature. An assessment of techniques of analysis frequently used in these studies was initiated to determine their adequacy for use in the NINCDS survey of major neurological disorders in Copiah County, Mississippi (Y01-NS-70031, N01-NS-7-2387).		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02406-01 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) The Frequency of Neurological Disorders Among Hospital Discharges		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Herbert M. Baum, Ph.D., Survey Statistician, OBE, NINCDS		
COOPERATING UNITS (if any) Dr. Donald Smith, Hospital Care Statistics Branch, NCHS		
LAB/BRANCH Office of Biometry and Epidemiology, OD, NINCDS		
SECTION Section on Surveys and Demographic Studies		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .05	PROFESSIONAL: .03	OTHER: .02
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This is the first report of what is to become an annual reporting system. The Hospital Care Statistics Branch has agreed to provide us with data on hospital discharges where a neurological disorder is indicated. A list of ICDA codes has been prepared of conditions of primary interest to the Institute. By examining the data on the first discharge diagnosis and on all listed discharge diagnoses we intend to examine the time trends. In addition, by constantly updating the data we intend to be able to handle requests for data on the hospitalization of neurological conditions.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02237-03 OBE
PERIOD COVERED <p style="text-align: center;">October 1, 1978 through September 30, 1979</p>		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Development and Design of a Pilot Study for a National Survey of Epilepsy</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="margin-left: 40px;"> PI: Dallas Anderson, Survey Statistician, Section on Disease Statistics Surveys, OBE, NINCDS Other: Frederic Weinfeld, Head, Section on Disease Statistics Surveys, OBE, NINCDS </div>		
COOPERATING UNITS (if any) <div style="margin-left: 40px;"> W. Allen Hauser, Dept. of Neurology, St. Paul-Ramsey Hospital, St. Paul, Minn. 55101 Joseph Steinberg, Survey Design, Inc. </div>		
LAB/BRANCH <div style="margin-left: 40px;">Office of Biometry and Epidemiology</div>		
SECTION <div style="margin-left: 40px;">Office of the Chief</div>		
INSTITUTE AND LOCATION <div style="margin-left: 40px;">NINCDS, NIH, Bethesda, Md. 20205</div>		
TOTAL MANYEARS: <div style="text-align: center;">.70</div>	PROFESSIONAL: <div style="text-align: center;">.50</div>	OTHER: <div style="text-align: center;">.20</div>
CHECK APPROPRIATE BOX(ES) <div style="margin-left: 20px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="margin-left: 20px;"> <input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <div style="margin-left: 40px;"> <p> This pilot was initiated to develop a new and untried method of ascertain- ing the <u>incidence and prevalence of epilepsy</u>. The previously used methods have serious deficiencies and this proposal seeks to remedy them. The goal is to use <u>pharmacies</u> filling anticonvulsive prescriptions to lead to the physicians providing care and thus to the <u>epileptics</u>. By using nationwide <u>probability</u> <u>sampling techniques</u>, valid estimates of the U.S. epileptic population should be made. The contract was let and the pilot study is about to get underway. </p> </div>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02238-03 OBE
PERIOD COVERED <p style="text-align: center;">October 1, 1978 through September 30, 1979</p>		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Pilot Data Bank Project Network in Stroke (previously titled: Computerized Interactive Data Bank for Comprehensive Stroke Centers)</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Selma C. Kunitz, Head of Section on Systems Design and Data Processing OBE, OD, NINCDS Other: Cynthia Gross, Ph.D., Biostatistician, SSDDP, OBE, OD, NINCDS Barbara Nichols, Programmer, SSDDP, OBE, OD, NINCDS Sylvia Edelstein, Systems Analyst, SSDDP, OBE, OD, NINCDS Dr. Albert Heyman, Duke University Medical Center Dr. Jay Mohr, University of South Alabama College of Medicine Dr. Thomas Price, University of Maryland School of Medicine Dr. Philip Wolf, Boston University Medical Center, School of Medicine		
COOPERATING UNITS (if any) Duke University Medical Center; Univ. of Maryland, School of Medicine; University of South Alabama, College of Medicine; Boston University Medical Center, School of Medicine		
LAB/BRANCH <p style="text-align: center;">Office of Biometry and Epidemiology</p>		
SECTION <p style="text-align: center;">Systems Design & Data Processing</p>		
INSTITUTE AND LOCATION <p style="text-align: center;">NINCDS, NIH, Bethesda, Md. 20205</p>		
TOTAL MANYEARS: <p style="text-align: center;">1.5</p>	PROFESSIONAL: <p style="text-align: center;">1.2</p>	OTHER: <p style="text-align: center;">.3</p>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p> A goal of developing a <u>computerized interactive data bank</u> for the Comprehensive Stroke Centers is to provide a development model for neuro- logical diseases which will aid both the clinician and researcher in the treatment, prognosis, rehabilitation, and possible prevention of such diseases. The objectives of the project are: a. <u>To develop a uniform method of data collection</u> utilizing standard clinical nomenclature and vocabulary, patient histories, diagnosis, and treatment. b. <u>To implement an interactive compre- hensive data bank network</u> enabling pooling of clinical data among institutions, collaborative inter-institutional studies, rapid access to large quantities of clinical data, and computer consultation. c. <u>To demonstrate the feasibility</u> of such a network, including the computer aspects, the collaboration among a number of institutions, to serve as a model for neurological diseases and disorders. </p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02239-03 OBE
PERIOD COVERED <p style="text-align: center;">October 1, 1978 through September 30, 1979</p>		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Design of Convulsive Disorder Questionnaires</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <p style="text-align: center;">PI: Frederic Weinfeld, Chief, Surveys and Demographic Studies Section, OBE, NINCDS</p>		
COOPERATING UNITS (if any) Clint Burnham, Health Interview Survey, NCHS W. Allen Hauser, Dept. of Neurology, St. Paul-Ramsey Hospital St. Paul, Minn. 55101		
LAB/BRANCH <p style="text-align: center;">Office of Biometry and Epidemiology</p>		
SECTION <p style="text-align: center;">Office of the Chief</p>		
INSTITUTE AND LOCATION <p style="text-align: center;">NINCDS, NIH, Bethesda, Md. 20205</p>		
TOTAL MANYEARS: <p style="text-align: center;">.5</p>	PROFESSIONAL: <p style="text-align: center;">.5</p>	OTHER:
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p>The design and field testing of <u>questionnaires</u> to be used as a supplement to the NCHS Health Interview Survey (HIS). The first was designed to determine the persons with some degree of <u>stroke</u>, diagnosed or undiagnosed; and hospitalization. This questionnaire was included in the 1977 HIS. A second has been designed to measure those persons with <u>convulsive disorder</u> and is being proposed for the 1978-79 HIS. The stroke questionnaire has been submitted to NCHS and is included in their current household interview survey.</p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02340-02 OBE
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Pilot Data Bank Network Project in Coma		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Selma C. Kunitz, Head of Section on Systems Design & Data Processing, OBE, OD, NINCDS Other: James M. Dambrosia, Ph.D., Mathematical Statistician, Section on Mathematical Statistics, OBE, OD, NINCDS Cynthia Gross, Ph.D., Biostatistician, SSDDP, OD, NINCDS Sylvia Edelstein, Systems Analyst, SSDDP, OD, NINCDS Barbara Nichols, Programmer, SSDDP, OD, NINCDS Dr. Lawrence Marshall, University Hospital at San Diego, CA Dr. Robert Grossman, University of Texas Medical Branch at Galveston, Texas Dr. John Jane, University of Virginia Medical Center, Charlottesville, Virginia Dr. Douglas Miller, Medical College of Virginia, Richmond, VA		
COOPERATING UNITS (if any) University Hospital at San Diego, CA; University of Texas Medical Branch at Galveston, Texas; University of Virginia Medical Center, Charlottesville, VA; Medical College of Virginia, Richmond, VA		
LAB/BRANCH Office of Biometry and Epidemiology		
SECTION Systems Design and Data Processing		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .8	PROFESSIONAL: .6	OTHER: .2
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A <u>pilot multi-centered interactive data bank project</u> restricted to <u>traumatic coma</u> has been implemented. The objectives of the study are: 1. To utilize a uniform clinical vocabulary and method of data input 2. To evaluate the feasibility of a multi-centered traumatic coma data bank system to examine: a. The ability of diverse institutions to participate and collaborate effectively b. The ability to collect data of high quality c. The ability to insure the quality and quantity of data from diverse institutions d. The preliminary utility of the data for patient management and in indicating research leads e. The ability to provide guidelines and protocols for expansion to additional centers and other neurologic disorders.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02348-02 OBE
PERIOD COVERED <p style="text-align: center;">October 1, 1978 through September 30, 1979</p>		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Simulated CAT Display</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Alan J. Talbert, Mathematical Statistician, OBE, NINCDS P.I.: Rodney Brooks, Physicist, SN, NINCDS		
COOPERATING UNITS (if any) <p style="text-align: center;">Neuroradiology and Computed Tomography Section, SN, NINCDS</p>		
LAB/BRANCH <p style="text-align: center;">Office of Biometry and Epidemiology</p>		
SECTION <p style="text-align: center;">Mathematical Statistics</p>		
INSTITUTE AND LOCATION <p style="text-align: center;">NINCDS, NIH, Bethesda, Maryland 20205</p>		
TOTAL MANYEARS: <p style="text-align: center;">.2</p>	PROFESSIONAL: <p style="text-align: center;">.2</p>	OTHER:
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 30%;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS </div> <div style="width: 30%;"> <input type="checkbox"/> (b) HUMAN TISSUES </div> <div style="width: 30%;"> <input type="checkbox"/> (c) NEITHER </div> </div> <div style="display: flex; justify-content: space-between; align-items: flex-start; margin-top: 5px;"> <div style="width: 30%;"> <input type="checkbox"/> (a1) MINORS </div> <div style="width: 30%;"> <input type="checkbox"/> (a2) INTERVIEWS </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p>A method was devised to simulate <u>CAT scans</u> of phantom subjects on a local printer. This eliminated a lengthy procedure involving writing and transferring tapes to and from an <u>EMI scanner</u> in a remote building. The new procedure reduces the turnaround time for CAT experiments from hours to minutes, greatly speeding up research in interpolation methods and aliasing errors in image reconstruction.</p> <p style="text-align: center; margin-top: 20px;">Early in fiscal year 1979 the work was brought to a conclusion.</p>		

ANNUAL REPORT

October 1, 1978 through September 30, 1979

Extramural Activities Program
National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
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Director's Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Extramural Activities Program (EAP), NINCDS, was organized in July, 1975, to serve as the Institute center for science administration and fiscal management of the grant, fellowship, and research contract programs. The structure of EAP includes components responsible for manpower, scientific merit review, contract management, grants management, committee management, data reporting and analysis, and program support services including processing.

The senior staff of EAP consists of:

- Director
- Deputy Director (Research Grants)
- Assistant Director for Manpower Programs
- Chief, Scientific Evaluation Branch
- Chief, Contracts Management Branch
- Chief, Grants Management Branch
- Chief, Office of Data Analysis and Reports

Staff carries out an overall coordinating and supervisory function in regard to the implementation of recommendations of the NANCDS Council and Contract Advisory (TMR) Committees, and the processing and issuance of proposals and awards in the respective program areas. The Director, EAP, in consultation with the Director of NINCDS, works closely with the other Program Directors on questions of policy.

More specifically, the Extramural Activities Program coordinates grant and contract programs for the NANCDS Council, the Program Directors, the Contract Review Board, the Training Board, the Program Staff, and the Extramural Staff. The EAP studies and supervises certain program processes, e.g., distribution of awards during the four quarters of the fiscal year; prepares summary data, e.g., the Research Grant and Fellowship Data Books; and provides fiscal information, e.g., Fiscal Status Reports, Percentage Funding Rates, and develops alternative strategies for various budget levels.

The only major change in personnel during the past year was that Dr. John C. Dalton, formerly Deputy Associate Director, Program Activities, NIGMS, was appointed Director of the EAP. Hopefully, this portends a stabilized period of development for EAP which, through a variety of circumstances, has been plagued by numerous changes in leadership for the past several years.

In summary, the Extramural Activities Program provides for the Director of the Institute and the Directors of the Program Areas, scientific, fiscal, and administrative management support services.

ANNUAL REPORT
October 1, 1978, through September 30, 1979
Research Grants Program
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Research Grants portion of the NINCDS Annual Report is intended as an overall summary of administrative, logistical and personnel problems and developments as they pertain to research grants. For purposes of cohesiveness, however, other activities (training awards, contracts, etc.) may be mentioned although they are discussed in more detail elsewhere.

The research grant, contract, and training programs of the NINCDS are focused on the identification, stimulation, and support of essential research problems aimed at the improved diagnosis, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, the ear, and human communication. They include disorders of the young (cerebral palsy, epilepsy, learning disabilities), of adulthood (head and spinal cord injury, multiple sclerosis, brain tumors), and of the aged (stroke, parkinsonism, otosclerosis). The administrative instruments used to accomplish these purposes include research projects, research program projects, clinical research centers, research career awards, research career development awards, teacher-investigator awards, institutional research fellowship awards, individual research fellowship awards, and contracts.

The following Table shows the number of research grant applications considered by the Council at its spring meetings in recent years:

<u>JUNE '74</u>	<u>JUNE '75</u>	<u>SEPT. '76*</u>	<u>MAY '77</u>	<u>MAY '78</u>	<u>MAY '79</u>
428	481	493	643	676	647

*Comparable to a spring meeting on the basis of the new fiscal year.

The number of applications reviewed has increased about 51 percent over the five-year period with rather regular gradual increases from year to year. This may partially be attributed to the effectiveness of the research training programs of the Institute from which the output of fully trained investigators has reached its full potential only in recent years. The very large increase in May, 1977, is probably due largely to the fact that for the previous year or two it was possible to fund only 25-30 percent of the approved applications. A large proportion of the unfunded applicants reapply, thus increasing the number of applications to be reviewed.

The following Table shows the number of research grants awarded and the total amounts of funds expended (in millions) each year for the past five years.

	<u>FY '75</u>	<u>FY '76</u>	<u>FY '77**</u>	<u>FY '78</u>	<u>FY '79</u>
NUMBER*	1,221	1,200	1,075	1,223	1,533
DOLLARS*	\$86.6	\$90.4	\$94.9	\$108.9	\$139.6

*Includes RCDAs and TIAs **Exclusive of Transition Quarter

From FY '75 to FY '78 there was a gradual increase in the funds available. However, the number of grants awarded did not increase, presumably because of inflation, increases in indirect costs, and other increases in the cost of doing research. For the current year (FY '79) there was an increase of 28.3 percent in the amount of funds available and an increase of 25.3 percent in the number of grants awarded.

Table I shows the number of awards and the amounts of funds expended for each type of award within each Program Area.

TABLE I

Number of Awards and Dollars * Expended by Program Area and Type of Award

<u>TYPE OF AWARD</u>	<u>PROGRAM AREAS</u>								<u>TOTAL</u>
	<u>No.</u>	<u>CD</u> <u>Dollars</u>	<u>No.</u>	<u>FN</u> <u>Dollars</u>	<u>No.</u>	<u>ND</u> <u>Dollars</u>	<u>No.</u>	<u>ST</u> <u>Dollars</u>	<u>No.</u> <u>Dollars</u>
Research Grants (R01)	257	16.849	376	23.735	497	35.551	160	12.222	1290 88.357
Program Projects (P01) and Clinical Centers (P50)	16	7.000	10	2.763	25	13.864	28	17.648	79 41.275
Contracts (N01)	18	1.400	17	2.253	16	7.648	16	3.005	67 14.306
Training Grants (T32)	15	.751	12	.699	20	1.051	5	.242	52 2.743
Fellowships (F32)	68	1.226	71	.964	130	2.095	24	.337	293 4.622
Teacher Investigator Awards (K07)	16	.628	1	.041	31	1.282	11	.460	59 2.411
Research Career Development Awards (K04)	20	.723	23	.796	48	1.737	9	.308	100 3.564
Research Career Awards (K06)	1	.034	-	-	3	.097	1	.031	5 .162
GRAND TOTAL	411	28.611	510	31.251	770	63.325	254	34.253	1945 157.440

*Dollars\$ in millions

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ANNUAL REPORT
October 1, 1978, through September 30, 1979
Assistant Director for Manpower Programs' Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Institute has four training programs. Two programs, National Research Service Awards for Institutional Grants (training grants) and National Research Service Awards for Individual Postdoctoral Fellows (fellowships), are funded from \$7.365 million available in the FY '79 budget for training. The other two programs, the Research Career Development Award Program and the Teacher Investigator Development Award Program, are funded from FY '79 funds available for research grants.

A major development during the year was the approval of Title II, P.L. 95-622, Biomedical Research and Research Training Amendments of 1978, on November 9, 1978. This is the enabling legislation for the National Research Service Award Programs and it authorized a number of significant modifications in the training grant and fellowship programs.

One of the major new activities authorized was support for "short term" training, three months or less, without accruing a payback obligation. In anticipating favorable Congressional action on this matter, two applications were received for the support of summer training programs, both of which received high technical merit ratings and were funded. Another type of program that could come under this new short term training authority is that which might be developed for medical students who would receive three months of research training in free or off quarters during their medical training. Support for this type of short term training is currently under consideration by the NIH.

The enabling legislation deleted the requirement that the National Advisory Council review fellowship applications. With this change, beginning with the January 1979 review cycle, NRSA fellowship applications (F-32s) received their secondary review by the NINCDS Training Board. Ultimate decisions regarding the funding of NRSA fellowship applications are now the responsibility of the Training Board.

National Research Service Awards for Institutional Grants (Training Grants)

From FY '79 funds, the Institute provided continuation support for 36 NRSA programs and made 19 new and renewal awards and two phase-out supplements. NINCDS made awards to support the following number of programs, according to NINCDS Program Area:

Program Area	New, Renewal & Supplemental Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	2	\$.102	13	\$.649	15	\$.751
Fundamental Neurosciences	9	.460	6	.383	15	.843
Neurological Disorders	5	.147	15	.904	20	1.051
Stroke and Trauma	3	.136	2	.106	5	.242
Total	19	\$.845	36	\$2.042	55	\$2.887

*Amounts in thousands

In the training grant program, funds are being provided for 57 predoctoral trainees and 200 postdoctoral trainees. In addition, about 72 short term trainees were supported in summer programs.

Since the initiation of the National Research Service Award programs, FY '79 was the first year any training grant programs were considered for renewal support. Although five programs terminated on June 30, 1979, only four applied for renewal support, two of which did not receive good enough priorities to compete successfully. These two programs received phase-out support for those trainees who had initiated their training and whom the program directors felt a commitment to continue to support.

National Research Service Awards for Individual Postdoctoral Fellows (Fellowships)

From FY '79 funds, the Institute provided continuation support for 152 fellows and made 185 new and renewal awards. A number of supplemental awards were also made but this did not increase the number of individuals being trained. NINCDS made awards to support the following number of fellows, according to NINCDS Program Area:

Program Area	New, Renewal & Supplemental Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	39	\$.530	36	\$.496	75	\$1.026
Fundamental Neurosciences	63	.806	39	.504	102	1.310
Neurological Disorders	62	.779	70	.977	132	1.756
Stroke and Trauma	21	.283	7	.103	28	.386
Total	185	\$2.398	152	\$2.080	337	\$4.478

*Amounts in thousands

Research Career Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation RCDAs, according to NINCDS Program Area:

<u>Program Area</u>	<u>New Awards</u>		<u>Continuation Awards</u>		<u>Total</u>	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	2	\$.070	20	\$.698	22	\$.768
Fundamental Neurosciences	2	.062	21	.737	23	.799
Neurological Disorders	7	.231	47	1.551	54	1.782
Stroke and Trauma	<u>3</u>	<u>.094</u>	<u>8</u>	<u>.285</u>	<u>11</u>	<u>.379</u>
Total	14	\$.457	96	\$3.271	110	\$3.728

*Amounts in thousands

Teacher Investigator Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation TIDAs, according to NINCDS Program Area:

<u>Program Area</u>	<u>New Awards</u>		<u>Continuation Awards</u>		<u>Total</u>	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	8	\$.330	8	\$.306	16	\$.636
Fundamental Neurosciences	0	0	0	0	0	0
Neurological Disorders	12	.496	21	.922	33	1.418
Stroke and Trauma	<u>9</u>	<u>.357</u>	<u>3</u>	<u>.120</u>	<u>12</u>	<u>.477</u>
Total	29	\$1.183	32	\$1.348	61	\$2.531

*Amounts in thousands

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Grants Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Grants Management Branch (GMB) consists of two sections, the Grants Administration Section and the Grants Processing Section. The Grants Administration Section consists of seven people and the Grants Processing Section consists of fifteen people.

During fiscal year 1979, the GMB was responsible for a grant budget in excess of \$144 million, of which approximately \$135 million was for research and \$7 million was for training. Compared to fiscal year 1978, this represented a 21% increase in the total grant budget and a 23% increase in the research budget while the training budget remained constant. From the fiscal year 1979 grant budget, it is anticipated that approximately 2,000 awards will be made which would represent an increase of 11% in the total number of awards.

During fiscal year 1979, the GMB increased its interaction with the Scientific Evaluation Branch (SEB) through both sections of the GMB. The Grants Processing Section now provides the SEB with the correct recommended amounts for the Teacher Investigator Development Award program. The Grants Administration Section now administratively reviews each program project and center application prior to its site visit and provides SEB with a written report of this review. This report is for use by the Executive Secretary and the fiscal consultant before and during the site visit. After the site visit the site visitors' budgetary recommendations are reviewed and accurate recommended budgets are determined.

The GMB has increased its interaction with the other extramural programs by providing, upon request from the programs, grants management advice to potential applicants responding to a Program Announcement or Requests for Applications (RFAs).

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Contracts Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Contracts Management Branch (CMB) consists of the Contracting Officer, who is Chief of the Branch, three contract specialists, and four supporting staff members.

During the fiscal year 1979, the CMB was responsible for some 100 research contracts and Interagency Agreements, totaling \$19.5 million. In addition, there are 90 research contracts in various stages of being closed-out administratively.

The CMB expects to award approximately 18 new contracts during FY 1979. Added to this workload are 70 renewals of existing contracts and over 100 actions modifying contracts in some other manner not involving funds.

The CMB has been coordinating the training of NINCDS Project Officers in accordance with the Department-wide requirement for training of Program personnel serving in this capacity. Over half of the Institute's Project Officers have now received the required training.

The DHEW began a Contracting Officer Certification Program in May, 1977, which requires all contract specialists to be certified by the Department by October 1, 1980. All contract specialists in the NINCDS have been certified.

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October 1, 1978, through September 30, 1979
Office of Data Analysis and Reports
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Office of Data Analysis and Reports continues to perform all the same functions as in the past and has added several new activities this year. One is the publication of "ODAR and YOU" - a booklet describing the reports and services available from the Office. Another is the completion of a computerized information system for contracts which is being used to issue recurring reports on both active contracts and Requests for Proposals.

The Office continues to publish on an annual basis the Training Data Book, the Fiscal Year Summary Book Series and the NINCDS Index to Research Grants and Contracts and on a semi-annual basis the Research Grants Data Book.

The programmer-trainee has completed her prescribed course work and on-the-job-training and is now filling a programmer slot in this office. One of the program analysts has moved to another institute and this vacancy will not be filled. The staff at present consists of three program analysts, two computer programmers, two grants clerks, and a clerk typist.

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October 1, 1978, through September 30, 1979
Scientific Evaluation Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Scientific Evaluation Branch (SEB) has the responsibility for the technical merit and scientific review of contracts, program projects, clinical research centers, Institutional National Research Service Awards, Teacher Investigator Development Awards and many conference grants. The Communicative Disorders Review Committee, Neurological Disorders Program Project Review A Committee, Neurological Disorders Program Project Review B Committee, and Special Review Committee are components of the SEB and provide the initial technical merit and scientific review of the proposals for the Institute staff, Contract Review Board and the Institute National Advisory Council.

The SEB reviewed a total of 181 grant applications for FY '79 Advisory Council meetings. This represents a 68% increase over the number of applications (108) reviewed during the previous fiscal year. Sixty-six of the 181 applications involved site visits. This represents a 61% increase over the number of site visits (41) conducted in the previous year, and reflects a higher proportion of program project-type applications received. In addition to these reviews, the SEB conducted technical merit reviews of contract proposals for 16 Requests for Proposals during FY '79. This figure is somewhat less than for the previous year and is attributable to a decline this year in the use of the contract funding mechanism by the Institute; however, estimates indicate that significantly more contracts will be reviewed in FY '80.

The SEB has established liaison with the Intramural Program, the Communicative Disorders Program, the Fundamental Neurosciences Program, the Neurological Disorders Program, and the Stroke and Trauma Program to facilitate the technical merit and scientific review of contracts, grants and conferences. Typical coordinating efforts here include appearances by the SEB staff at workshops sponsored by the above mentioned programs for prospective grant applications (e.g., for Requests for Applications) for the purpose of providing guidance on application preparation and review procedures. The SEB also participates in NIH-wide review study groups in order to achieve uniformity and update peer review procedures appropriately and promptly. The SEB maintains a continuing liaison with leaders of the scientific community for the purpose of identifying the most qualified persons to serve on the SEB panels and committees.

The attached Table summarizes the numbers and types of applications reviewed in FY '78 and FY '79.

NINCDs RESEARCH AND TRAINING GRANTS REVIEWED BY THE SCIENTIFIC EVALUATION BRANCH
FISCAL YEARS 1978-1979 BY GRANT TYPE AND COUNCIL DATE

	Oct. '77	Feb. '78	June '78	TOTAL		Oct. '78	Feb. '79	June '79	TOTAL	
				FY '78	FY '79				FY '79	FY '79
P50s	6* (2)	17 (15)	6 (5)	29 (22)	14 (12)	11 (9)	21 (15)	46 (36)		
P01s	8 (7)	2 (2)	5 (5)	15 (14)	6 (6)	3 (3)	6 (6)	15 (15)		
RFAs	-	-	4 (4)	4 (4)	-	-	19 (7)	19 (7)		
R10/R13s	2 (0)	3 (0)	3 (0)	8 (0)	3 (2)	1 (0)	7 (2)	11 (4)		
T32s	12 (1)	6 (0)	3 (0)	21 (1)	9 (0)	27 (4)	8 (0)	44 (4)		
KO7 (TIDAS)	9	7	15	31	18	9	19	46		
TOTALS	37 (10)	35 (17)	36 (14)	108 (41)	50 (20)	51 (16)	80 (30)	181 (66)		

*Total number of Applications indicated by the first number.

-Site visits indicated by the number in parentheses.



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Communicative Disorders Program

National Institute of Neurological and Communicative Disorders and Stroke

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Vestibular (Balance)	12
Laryngeal	14
Communicative Aids	15
Language	17
Speech	19
Touch	22
Taste	23
Smell	25
CONTRACT NARRATIVES	
Development of a Research Tool Concerning Speech and Language Therapy for Aphasic Adults Y01 NS 4-0019	27
Study of Auditory Sensitivity in Young Children N01 NS 5-2313	29
Study of Estimators of Aphasic Patients' Communicative Performance in Daily Life N01 NS 5-2317	31
Measures of Children's Language Performance N01 NS 5-2322	33
Study of Sensory and Perceptual Functioning of Young Children With and Without Delayed Language Development N01 NS 5-2323	35
Evaluation of Procedures for Screening Preschool Children for Signs of Impaired Language Development N01 NS 6-2353	37

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Feasibility of Use of Acoustic Analysis for Detecting Signs of Vocal Pathology Y01 NS 7-0033	39
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Decongestant/Antihistamine Therapy for Otitis Media with Effusion (OME) N01 NS 8-2384	45
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Early Identification of Drug-Induced Ototoxicity Z01 NS 02336-02 CDP	61
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Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

Introduction

The Communicative Disorders Program of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is responsible for research and training directed toward understanding the processes and structures subsumed for hearing, balance, language, speech and the special senses. The diagnosis, treatment and prevention of communication disorders is the program goal. Disorders involving the special senses of taste, smell, touch and pain relating to human communication are a part of the Communicative Disorders Program.

Disorders of human communication are not usually the primary cause of death and they do not receive the same attention as cancer, stroke or heart disease; however, the communicative disorders are one of the most frequent disabilities in our society. Approximately fifteen million individuals in this country have a hearing loss severe enough to impair their ability to function in everyday activities and ten million persons do not speak normally. An additional number do not have adequate language to communicate effectively. Communicative disorders create an economic impact on the Nation when their habilitative, rehabilitative, and special education costs are considered. An even more important consideration is the effect of such handicaps upon the quality of life of the individuals.

Communicative Disorders Staff and Environment

Dr. J. Buckminster Ranney was appointed Deputy Director of the Program in September 1978. In January 1979 the Director of NINCDS selected Dr. Ralph F. Naunton, Professor of Surgery and former Director of the Division of Otolaryngology at the University of Chicago, as the Director of the Communicative Disorders Program. Dr. Naunton will assume his responsibilities in September 1979. The tragic death of Dr. Irving Woods in February 1979 has created a void in the Program staff; Dr. Woods' replacement will be recruited in the fall of 1979. Dr. Barbara Reiner has accepted a temporary appointment as an Information Specialist Expert Consultant to guide the MEDLARS project. A chemosensory scientist has been identified. The individual, the institution and the Institute are exploring the potential of an Interagency Personnel Agreement (IPA) appointment.

Dr. Rolf F. Ulvestad has responsibility for the otolaryngology portion of the Program. He serves as a contract project officer, and he also supervises the consultant and residency ear, nose and throat service at the Clinical Center.

Dr. Christy Ludlow, Speech Pathologist, directs the speech and language portion of the Program. In addition to her extramural activities, she maintains a clinical research program with the assistance of Mrs. Celia Cardano, a full-time research Speech Pathologist.

The areas of communicative aids, effects of noise on hearing, and management of hearing disorders are the responsibility of Dr. Earleen Elkins, an Audiologist. She also supervises the Audiology Service of the Clinical Center and directs clinical research with the assistance of Mrs. Anita Pikus, Audiologist.

The adjustment of space in the Federal Building will serve the Program. The research and clinical activities continue to be hampered by inadequate space and facilities. Since no testing space is available for use in the Clinical Center, patients must be accompanied by staff to and from Building 36 for testing in one of the three rooms available for speech and language research. Although this setting is safe for conducting patient speech and language testing, it is often distracting to subjects, and a great deal of time is lost since the staff must continuously dismantle and reassemble instrumentation each time a subject is tested due to severe space limitations. A sound controlled room which can be permanently set up for conducting speech and language patient testing is badly needed in the Clinical Center. Clinical needs for otolaryngology and audiology at the Clinical Center have remained largely unimproved for reasons beyond the control of the Communicative Disorders Program. The Clinical Center has agreed to build, equip and staff at an appropriate level, an adequate facility to meet present clinical testing needs in audiology.

Program Activities

Activities of the Communicative Disorders Program this year include:

- 1) Ad Hoc Program Advisors Meetings
- 2) Implementation of National Research Strategies
- 3) Clinical Research Activities
- 4) Program and Investigator Conferences
- 5) Demonstration of Bibliographic Services for Clinicians and Investigators in Communicative Disorders
- 6) Development of Program Announcements
- 7) Development of Requests for Proposals

The Ad Hoc Program Advisors met twice this year, in September 1978 and April 1979. The members of the group for FY 1979 include:

Katherine S. Harris, Ph.D.
Graduate School of University Center of the City University of
New York

Ira J. Hirsh, Ph.D.
Central Institute for the Deaf, St. Louis

Marcel Kinsbourne, M.D., Ph.D.
Hospital for Sick Children, Toronto

David J. Lim, M.D.
University Hospital, Ohio State University, Columbus

Ralph F. Naunton, M.D.
The Pritzker School of Medicine, University of Chicago

James B. Snow, Jr., M.D.
University of Pennsylvania, Philadelphia

The Advisors have provided direction for future research and areas needing special emphasis. They have also critically evaluated staff suggestions for new or special initiatives and approved or suggested alternatives. The next meeting is scheduled for October 1979.

Dr. Ludlow and Dr. Reiner have upgraded MEDLINE services for specialists in communicative disorders. Over 100 additional terms have been added which greatly improves the specificity of searches and the capability to retrieve information. Several journals have been added to the data base to improve coverage. A MEDLINE Users' Manual and Thesaurus will be published in September 1979 and made available to investigators in the field. Drs. Ludlow and Reiner will present workshops at professional meetings to assist scientists and clinicians in communicative disorders to meet their information needs through MEDLINE.

Dr. Ludlow organized a working conference including otolaryngologists, speech scientists, and electrical engineers to review recent technological developments in the field of laryngeal pathology. The purpose was to identify research areas of greatest potential for the development of methods for the assessment of vocal pathologies. Several methods were identified, reviewed, and discussed for the assessment of normal and pathological laryngeal function including fiberoptic, electromyographic, airflow, acoustic and laryngographic assessment. The proceedings of the conference will be published as a monograph early in 1980 and widely disseminated to persons in the field.

Dr. Elkins has cooperated with the National Institute of Aging in sponsoring a seminar on "Hearing Impairment in the Aging Population." Following this seminar, a group of interdisciplinary scientists was assembled to address the specific problem of prosthetic devices for the aged individual with impaired hearing. Both conferences were designed to provide programmatic direction for both sponsoring Institutes.

The proceedings of the Communicative Disorders Program sponsored workshop on "Otitis Media and Child Development" (held in FY 78) have been co-edited by Drs. Ulvestad and Hanson and will be published as a supplement to the September 1979 Annals of Otolology, Rhinology and Laryngology.

Clinical Activities

The consultation services in otolaryngologic problems provided to the Clinical Center by Dr. Ulvestad have expanded during FY 79. In collaboration with the Department of Otolaryngology of the National Naval Medical Center, a senior resident from the Naval Otolaryngology program is now assigned to the Clinical Center under the supervision of Dr. Ulvestad. This has increased the flexibility of the service and established more direct lines of referral for intramural research in communicative disorders. Dr. Ulvestad provides medical/otolaryngological evaluations of subjects in the study of Acoustic Analysis of Vocal Pathology directed by Dr. Ludlow.

The Clinical Center program in hearing directed by Dr. Elkins provides services for hearing evaluation and treatment of patients under the care of attending physicians within the NINCDS and other Institutes. These patients have provided unique opportunities to develop descriptive hearing profiles for Wegener's granulomatosis, Cogan's syndrome, midline granuloma, ototoxic effects of chemotherapeutic agents, osteogenesis imperfecta, and chronic meningitis and meningioma. In addition, new methods are being studied for the early detection of ototoxicity in the hope that severe high-frequency hearing impairments may be prevented in patients on certain drug protocols. Documentation of accompanying hearing loss in the other clinical entities also provides valuable information for the management of these patients.

Clinical speech and language research has continued under the direction of Dr. Ludlow in collaboration with intramural scientists in the National Institute of Neurological and Communicative Disorders and Stroke and the National Institute of Mental Health. The research has the long-term goal of identifying neurochemical treatments for various speech and language disorders. The highlights of the research are the development of acoustic methods for identifying early signs of oral tardive dyskinesia in speech production; the assessment of laryngeal dysfunction in Shy Drager's syndrome; the evaluation of treatment of language-impaired hyperactive children with dextroamphetamine; the effects of stimulant drugs on auditory processing functioning in normalcy and pathology; and the assessment of neurological and neoplastic diseases of the larynx by automatic processing of laryngographic signals during speech.

Staff Activities

Dr. Ludlow served as Chairman, Scientific Affairs Committee of the American Speech-Language-Hearing Association; Associate Editor for Articles, Asha (Journal of the American Speech-Language-Hearing Association); Editorial Consultant, Journal of Speech and Hearing Disorders, and Journal of Speech and Hearing Research; and Liaison Representative of the American Speech and Hearing Association to the American Association for the Advancement of Science.

Dr. Elkins was appointed to two committees of the American National Standards Institute to develop standards for 1) speech audiometry and 2) speech interference levels. She has recently completed an assignment on the American Speech-Language-Hearing Association's Committee on Speech

Audiometry and is a Consultant Editor for the Journal of Speech and Hearing Research. She serves on the National Aeronautics and Space Administration's Executive Review Committee on Devices for the Hearing-Impaired, as a member of the Federal Panel for Research on the Effects of Noise, and the NINCDS representative for CHABA (Committee on Hearing, Bioacoustics, and Biomechanics).

Dr. Ulvestad represented NINCDS at a meeting with the Association of Academic Departments of Otolaryngology and the Society of University Otolaryngologists. He participated as faculty in the 13th Colorado Otology/Audiology Workshop and represented the Communicative Disorders Program at the combined Otolaryngology Spring Meetings and American Academy of Otolaryngology. He participated in the Otitis Media Research Planning Conference held in conjunction with the Second International Symposium on Otitis Media.

Staff Publications

Ludlow, C. L., Rapoport, J. L., Cardano, C. B., & Mikkelsen, E. J. Differential effects of dextroamphetamine on language performance in hyperactive and normal boys. In R. M. Knights and D. J. Bakker (Eds.), Treatment of Hyperactive and Learning-Disordered Children: Current Research. Baltimore: University Park Press, 1979.

Ludlow, C. L., Doran-Quine, M. E., (Eds.) The Neurological Bases of Language Disorders in Children: Methods and Directions for Research. NINCDS Monograph, Washington, D. C.: Government Printing Office, 1979.

Ludlow, C. L. Research directions and needs concerning the neurological bases of language disorders in children. In Ludlow, C. L. and Doran-Quine, M. E. (Eds.), The Neurological Bases of Language Disorders in Children: Methods and Directions for Research. NINCDS Monograph, Washington, D. C.: Government Printing Office, 1979.

Ludlow, C. L. Recovery and rehabilitation of adult aphasic patients: relevant research advances. In R. W. Reiber (Eds.), Communication Disorders. New York: Plenum Publishers, Inc., 1979, in press.

Reiner, B. J., and Ludlow, C. L. MEDLINE Users' Manual and Thesaurus for Specialists in Communicative Disorders. NINCDS, Washington, D. C.: Government Printing Office, 1979, in press.

Rapoport, J. L., Buchsbaum, M. S., Weingartner, H., Zahn, T., Ludlow, C. L., Mikkelsen, E., Langer, D. and Bunney, W. E. Dextroamphetamine: Cognitive and behavioral effects in normal and hyperactive children and normal adults. Archives of General Psychiatry, 1979, in press.

Ulvestad, R. F. Delayed meningitis following stapes surgery. Archives of Neurology. 36: 174-175, 1979.

Grants Activity Summary
Communicative Disorders Program

Hearing (Function)

Understanding of the normal mechanism of hearing is essential to the development of tests to evaluate the abnormal system and provide methods of managing the hearing-impaired. One NINCDS supported project is investigating three aspects of normal binaural processing: Interaction of interaural time and intensity, binaural processing of high-frequency waveforms, and binaural recognition of information presented in temporal sequences. The binaural processing of high-frequency waveforms has centered on filtered transients. Objective measures of signal energy provided the closest agreement on estimations of absolute and masked thresholds among filtered noise, sinusoids and filtered transients. The thresholds for repeated transients appear to closely parallel the known functions for temporal integration of sinusoids. The work not only provided a means of measuring transient intensity, but also suggests an objective measure for those using transient signals as in the measure of brain stem auditory evoked potentials. Two studies were conducted which provide a parametric look at the binaural processing of filtered transients. The studies showed that 1) binaural processing of high-frequency transients is due either to low-frequency spread of energy or a low-temporal repetition, as when the transients are repeated, 2) high-frequency thresholds are not processed very well by the binaural system when the transients are embedded in noise, and 3) that the various methods used to study binaural processing of transients probably all are probing the same aspect of binaural function. Additional work using transient signals employs sinusoids with transient or sudden onsets. The ability of the binaural system to process these stimuli depends on information in the low-frequency regions of the spectrum. The work with binaural processing of transients underlines the importance of considering both the low-frequency spectral and temporal content of a stimulus.

Two NINCDS supported experiments designed to determine the properties of the neuron which may mediate time differences in sound stimuli are reported. In the first experiment binaural neurons of the central nucleus of the inferior colliculus were measured as a function of interaural time differences in high-frequency noise bands and transients. The second experiment extended the investigation of such neurons to conditions in which the stimuli consisted of two-tone complexes. The frequency separations and depths of modulation of the stimuli were independently varied. In both experiments, the stimulus levels were low and a low-pass masking noise was present so as to eliminate the possibility of stimulation by low-frequency distortion products. Over half of the neurons with best frequencies higher than 1.5 kHz were found to be sensitive to interaural time differences. For stimuli consisting of two-tone complexes, this sensitivity was reduced as the depth of modulation was reduced. Tone separations exceeding the estimated critical bandwidth did not lead to a reduction in time sensitivity, indicating that the mechanism for processing interaural time differences is independent of that for the critical band.

NINCDS studies of the pitch of complex tones have used two-component tones as stimuli. The usual finding is that a complex tone consisting of two adjacent upper harmonics of some missing fundamental (e.g., 1000 Hz and 1200 Hz, harmonics of 200 Hz) can evoke a pitch corresponding to the fundamental. Recent results have indicated that this pitch is unchanged if the stimulus is presented dichotically, one harmonic to each ear. On the basis of these results, the claim has been made that pitch is mediated centrally, at a level in the auditory system after which information from the two ears is combined.

NINCDS studies of sound localization have employed a method of limits which requires the listener to report when s/he begins to hear a change in the locus of the preceding tone as the level of the target tone is increased. Results show a clear frequency effect. As the frequency of the preceding 60-dB tone increases from 500 Hz to 930 Hz, the signal level must be raised from an average of 27 dB to 40 dB in order for it to affect sound locus. At frequencies from 1000 Hz upward, the required signal level decreases very rapidly. These results are for a 1000 Hz signal from either a loudspeaker 15° to the listener's left or to his right, with the preceding tone coming from a speaker directly in front. Both signal and preceding tone are 30 ms and their onset time difference was 20 ms. The precedence (Haas) effect is prominent. Results were similar with simultaneous onset, but the masking effect was reduced by 3 to 10 dB. When the preceding tone burst was replaced by a continuous tone against which the 1000-Hz signal was presented, a classical masking curve was obtained with a peak where the signal and masker had the same frequencies. So far none of the data suggests a critical-band effect.

A NINCDS study investigated the discrimination of tempo for a transition that either preceded or followed a steady formant, one of the areas of energy concentration of a vowel sound. Comparisons of discrimination were made for transitions of rising or falling frequency and with the steady formants at different frequencies (either 500, 1000, or 2000 Hz). In each trial, the slower tempo of the test transition stimulus was discriminated relative to the faster tempo of the reference transition stimuli. Among trials, the tempo of the reference transitions remained the same while the test transition tempo differed based on subjects (Ss) responses. Different test transition tempos were obtained by holding constant the transition frequency but varying transition duration. The Ss were 19 hearing-impaired students at Gallaudet College and five normal-hearing adults. The hearing-impaired Ss had long-term, moderate-to-severe sensorineural losses and were categorized by their pure tone threshold configurations into flat or sloping. For the impaired-hearing groups, tempo discrimination was generally better for both rising and falling transitions preceding the formant than for transitions following the formant. Over-all formant frequencies tempo discrimination was slightly higher for preceding than following transitions.

A NINCDS investigator reports that although earlier experiments had included tests of the discriminability of changes in the frequency, duration and level of individual components of tonal patterns, listeners had never been challenged to resolve changes along each of these dimensions in a single experiment. The resolution of natural sounds demands that

simultaneous attention be paid to all of the acoustic dimensions. It is especially important that the listeners be capable of attending to several acoustic dimensions under conditions of high-stimulus uncertainty. Results indicate that the effects of signal-dimension uncertainty on the resolution of the frequency, duration, and intensity of isolated tones are specific to individual listeners, and are relatively slight in all cases.

A difficult area of study is being addressed by a NINCDS investigator to explore the ability of experimental subjects to scale sensation magnitudes on an absolute scale with an individually fixed unit rather than on a ratio scale with an arbitrary unit. Successful scaling procedures are necessary in various types of sensory research. The study examined five predictions: 1) Different groups of subjects should produce approximately the same absolute magnitude-estimation of magnitude-production scales. 2) A scale determined by means of absolute magnitude production on one group of subjects should agree with a corresponding scale determined by means of absolute magnitude estimation on a different group. 3) The absolute scale should not depend on the subjects' experience in psychological scaling without designated standards. 4) The scale should not depend on the intensity of the first stimulus presented in absolute magnitude estimation or on the first number given in absolute magnitude production. 5) The scale should not depend on the intensity or number ranges used or available. All the predictions were verified experimentally and it is interesting to note that one experiment demonstrated that children who have learned numbers from 1 to 100 but do not know fractions, produce the same absolute scale as the adults, within the range of numbers available to them. Beyond the range of the available numbers, the scale is sharply truncated.

The long-term objective of one NINCDS study is to describe the role of the mechanical (fluid-elastic) activity of the cochlea in the processing of acoustic signals by developing an analytical model and supplementing it with laboratory experiments. The longstanding concern with "long" and "short" wavelengths in the cochlea seems to be almost settled, since most of the present workers on cochlear modeling now agree that both are present, with the short wavelengths dominant in the region of maximum response. For accurate modeling it has been necessary to include two, or better yet, three-dimensional fluid motion. An extensive analysis of the stiffness of the cochlear partition, including that of the primary spiral osseous lamina and the attachment of outer hair cell cilia to the tectorial membrane is reported. In all, four elastic modes are considered, two for the shearing deformation of the primary, one for the rotation of the arches of Corti, and one for the half-sinewave bulging of the pectinate zone of the basilar membrane. Some quantitative details are of interest. For example, the location of maximum response is insensitive to the degree of attachment of the cilia to the tectorial membrane, which eliminates one explanation for the cause of the observed post mortem change. Only when the model basilar membrane has zero stiffness in the axial direction is the rate comparable to that observed in the actual cochlea. Even a relative axial stiffness of only 10 percent is enough to cause the rate to be much slower than observed. The basilar membrane does consist primarily of transverse fibers. However, Bekesy, in his well-known point-load tests, reported a circular impression which would indicate a relative axial stiffness of at least 50 percent. In

similar stimulation of the basilar membrane in a post mortem preparation, the relative axial stiffness was difficult to quantify, but it most certainly is not zero.

A NINCDS study has shown that the dorsal cochlear nucleus and inferior colliculus are anatomically complex structures whose cells demonstrate a variety of response properties. A clear separation of these properties into one group associated with the principal cells of the nucleus and another associated with interneurons has been attained for the dorsal cochlear nucleus and will be sought for the inferior colliculus. The information about the connectivity of cells in the nuclei of the brainstem auditory system is a necessary step in the process of specifying the stimulus transformations occurring in those nuclei and the way in which the central nervous systems processes sound stimuli.

One NINCDS investigator stated that the discovery of a detailed highly-ordered reorganization of cortical fields as a result of loss of sensory input has potential significance. First, it indicates that a reorganization of cortical fields might occur as an unavoidable consequence of loss of sensory input. Second, this reorganization might follow predictable rules that would frustrate simple attempts at rehabilitation. For example, if a reorganization of the auditory cortex occurred that paralleled that observed in the somatosensory cortex, then application of an amplification hearing aid could result in totally unexpected perceptual distortions. If the perception arising from a sector of the cortex can change as a consequence of a change of connection, there could conceivably be less perceptual deficit resulting from the reorganization of connection.

Hearing (Disease)

A NINCDS grantee reported that the initial study of pathology and chronic human otitis media has been completed. Added temporal bones of human cases continued to be studied for all forms of otitis media. Tissue (mucosa) granulations and cholesteatoma were collected at the time of surgery for histochemical and electron-microscopic analysis in conjunction with the human subject protocol. Sequelae of otitis media were studied histologically and at exploratory tympanotomy. All studies in this project included histopathological assessment findings. A separate study included animal models. The continuum of gross and microscopic pathological changes of otitis media in the model were studied. Studies of the inner ear complications of otitis media and the role of the round window membrane continued. Sequential pathological changes of otitis media were described and quantified.

A NINCDS investigator obtained 196 middle ear effusions from 122 patients who ranged in age from five months to 12 years. Two main areas of research have been emphasized. One is to examine the possibility of IgE-mediated allergy in otitis media with effusion, and the other is to prove that the bacteria that were cultured from the middle ear effusions were the causative agent for inflammation in otitis media with effusion by means of demonstrating specific antibodies. In another study the intent was to see if allergy mediated by IgE is involved in otitis media with effusion by measuring IgE levels from a total of 138 middle ear effusions and paired

serum samples from patients with otitis media with effusion. The initial 62 paired specimens were assayed for IgE by the radioimmunosorbent test (RIST), and the later 76 paired specimens were assayed for IgE by the paper radioimmunosorbent test (PRIST). When the results obtained by these two techniques were compared, it was noted that the PRIST procedure gave significantly lower IgE values for effusions than the RIST method. When the effusion-to-serum ratios (E/S ratios) were computed from the PRIST data the E/S ratio was less than one, while RIST data gave an E/S ratio greater than one. The low E/S ratios (E/S 1.0) suggest that there may not be active secretion of IgE in the middle ear and thus do not support the conclusion previously reported by this and other laboratories. The results obtained with the PRIST procedure were confirmed by double antibody radioimmunoassay (RIA) for IgE. Thus, the PRIST procedure appears to measure the IgE content of middle ear effusions more accurately, and the results obtained by this procedure fail to support the concept of IgE-mediated allergy as a major causative factor in otitis media with effusion. However, because IgE is biologically active in trace quantities, the antibodies to bacterial antigens can be found in the effusions of children with acute suppurative otitis media.

With NINCDS support temporal bones from a patient with bilateral cochlear implants were studied. The patient was a 63 year old white male with acquired lues. The patient experienced sudden profound deafness on the left side 15 years prior to death, and a similar loss on the right side three years later. By the time of death he had carried a single induction coil in the right ear for three years and multiple (five) hard wire electrodes in the left ear for eight years. In the right ear supporting elements and numerous nerve fibers were present in the apical turn. The electrode on this side was apparently tolerated well, scala tympani was normal in shape and appearance. On the left side no nerve fibers were found in the osseous spiral lamina and there was extensive new bone formation in scala tympani. It is difficult to determine if, or to what extent, the implants were responsible for the severe sensorineural degeneration observed in both specimens. There was severe scarring and ossification of the posterior ampulla in both ears, in all likelihood resulting from the surgery. These specimens, as well as future "implant" bones which have been promised, provide important information about "implant" design and surgical techniques. Both implants were too long and deviated from their intended course in scala tympani and entered scala media 13mm from the round window niche. At the time of surgery the initial damage to the cochlear duct was probably considerable. In both specimens, however, the cochlear duct was intact enclosing the implants. Reissner's membrane showed no ruptures. Apparently healing and repair of the membranous walls occurred after surgery. The case strongly suggests that shorter implants or less deep insertion would be more advantageous and less damaging to the few nerve fibers which are present in the cochlea of "implant" candidates.

The purpose of one NINCDS study is to determine if human aminoglycoside ototoxicity can be predicted and, hence, prevented. The difference between Tobramycin and Gentamicin vestibular toxicity is statistically significant. Clinically, this is both an asset and liability for Gentamicin in that vestibular toxicity tends to develop early, before cochlear and/or definite

nephrotoxicity. The disadvantage of profound vestibular toxicity from Gentamicin is the devastating clinical syndrome produced (oscillopsia). At what level the subclinical evidence of vestibular toxicity (33 percent reduction in caloric nystagmus velocity) can be tolerated by an individual patient is not known. Hopefully, with the collection of further data, this factor will emerge. In patients who are well enough to undergo prospective electronystagmography monitoring, it appears that Gentamicin may become the drug of choice because of this early warning signal.

Vestibular (Balance)

A NINCDS investigator analyzed the postural control responses of normal human subjects and found that humans perform postural adjustments by moving the neck, hip and knee joints, as well as the ankle joint, and thus that the one-link model of body sway motion (which assumes motion only at the ankle joint) is inadequate. Humans seem to prefer ankle joint movement and control their posture primarily by this method when the control task is an easy one. However, individuals who have relatively poor postural control display prominent movements of other body joints, especially the hip. Individuals with good postural control also display movement of other joints when the control task is made more demanding by denying visual and proprioceptive cues. Non-vestibular sensors are somewhat frequency-selective. Denying vision produces instability primarily at lower frequencies (below 0.1 Hz), whereas denying proprioception produces instability primarily at higher frequencies (above 0.1 Hz).

NINCDS support was provided to study the characteristics of the human vestibulo-spinal control systems in the normal and vestibular-deficient human. Data was initially obtained from 204 children. Increased incidence of ear disease (e.g. serous effusions) does have an effect on vestibular responses. Five subjects with Tumarkin's otolithic crisis variant of Meniere's disease who underwent vestibular nerve section and seven patients with acoustic neuromas limited to the internal auditory canal were tested pre-operatively, one week and three months post-operatively. The results demonstrated significantly different adaptation patterns in acoustic neuroma as compared to the Meniere's disease subjects. Special permission was obtained to study a subject who had been implanted with the cochlear stimulation electrodes and who experienced body displacements when electrical stimuli were placed through his cochlear stimulating device. The subject demonstrated markedly different auditory, vestibulo-colic and vestibulo-spinal effects depending upon the electrode stimulated, the stimulus duration and the stimulus amplitude.

One NINCDS investigator reports that anatomical studies of the vestibular system provide the ability to recognize balance disorders and ultimately to treat them. A specific example of the value to recognition and treatment of vestibular disorders has been the proven effectiveness of posterior ampullary nerve transection in cases with benign paroxysmal positional vertigo. This procedure has now been used in ten patients to successfully alleviate the vertigo produced by stimulation of the posterior semi-circular canal. Other evidence is accumulating now to indicate that positional

vertiginous symptoms may arise from the other semi-circular canals. The demonstration of the types of eye movements that may be produced by stimulating these canals will be helpful in delineating other forms of positional vertigo.

Autoradiographic tracing technics for a NINCDS study indicated that primary vestibular fibers project ipsilaterally to: (1) All vestibular nuclei in a differential fashion, (2) cell group y, (3) the accessory cuneate nucleus, (4) parts of the reticular formation adjacent to the vestibular nuclei, and (5) parts of the cerebellar vermis (lobules IX and X) and flocculus. Primary vestibular afferents to the superior, medial, inferior and ventral part of the lateral vestibular nuclei were especially profuse, while vestibular projections to the cerebellum were rather modest. None of the isotope projected to nuclei known to receive secondary vestibular projections. There was no suggestion in this material of transneuronal transport of isotope. When isotope labeled cells in all parts of the spiral ganglion, radioactivity was seen in large parts of all cochlear nuclei. In addition, labeled axons entering the trapezoid body projected ipsilaterally to: (1) The lateral trapezoid nucleus, (2) the lateral superior olivary nucleus, (3) the dorsal dendritic zone of the medial superior olive, and (4) the pericollicular or cortical nucleus of the inferior colliculus. Isotope crossing the midline in fibers of the trapezoid body projected contralaterally to: (1) The medial trapezoid nucleus, (2) the ventral dendritic zone of the medial superior olive, (3) the ventral nucleus of the lateral lemniscus, and (4) the central nucleus of the inferior colliculus. Selective labeling of cells in the apical and middle ganglionic turns of the cochlea resulted in a similar pattern of centripetal transport, while selective uptake of amino acids by ganglion cells in the basal turn of the cochlea resulted in a considerable reduction in isotope transported to parts of the cochlear nuclei and to ipsilateral auditory relay nuclei related to the trapezoid body. No fibers of the trapezoid body were labeled contralaterally. Interpretation of these data raises the question of possible transneuronal transport in central auditory pathways. Two arguments suggested that isotope transport was not transneuronal: (1) The pattern of transport did not correspond to the demonstrated secondary projections of any individual cochlear nucleus, although it bears some resemblance to that described for the anteroventral cochlear nucleus; and (2) no similar transport is seen in the vestibular pathways.

A NINCDS investigator examined temporal bones demonstrating cochleo-saccular degeneration with collapse of the saccule and varying degrees of cochlear hydrops and degeneration. Two of these were from patients who had clear-cut history of hereditary deafness in their families and who were, themselves, deaf from birth or an early age. Another pair were from a man who became deaf in adult life, and had two grandsons who were deaf from birth. When one of the specimens was noted to have large clusters of purple-staining otoconia and otolithic membrane debris within the cochlear duct with tissue reaction about it, the other specimens were closely re-examined, and otoconia were found within the ductus reuniens and/or in the first portion of the cochlear duct. With this finding, a previously reported case, in 1974, was re-examined. This had been reported as "Saccule Degeneration and Ductus Reuniens Obstruction" and demonstrated a partially collapsed saccule with clusters of otoconia within the ductus reuniens which were

enclosed by dense fibrous tissue. There were also otoconia clusters in the first portion of the cochlear duct and hydrops of the cecum vestibulare but not of the rest of the cochlear duct. These cases are believed to represent varying degrees of degeneration of the cochlea in response to otoconial and otolithic membrane displacement from the saccule through the ductus reuniens. In some cases there was hydrops involving virtually the entire cochlea, whereas in others, there was hydrops of just the cecum vestibulare.

Laryngeal

A NINCDS study investigated the relationship between phonatory control and common segmental and suprasegmental errors of deaf speech. One EMG experiment examined deaf production of contrastive stress and intonation using laryngographic and EMG measures. Many investigators have noted that disorders of phonation are common in deaf speech. The pitch of the deaf is frequently reported as inappropriately high or low with respect to age and sex. In addition speech may be characterized by sudden pitch breaks or other evidence of inability to control voicing. There is some evidence that deaf children who are unable to sustain phonation are judged to have unintelligible speech. On the other hand, children with simple deviant overall pitch patterns (that is, pitch characterized as either too high or too low) are quite variable with respect to intelligibility. Thus, the relationship between phonatory control and intelligibility seems more complex than the general comments in the literature suggest.

A NINCDS investigator used inverse filtering techniques to obtain acoustic measures of laryngeal pathology from sustained vowel sounds. These measures, such as average pitch period or amplitude perturbation, may be applied to early detection of laryngeal pathology and to assessment of voice therapy techniques. A small homogeneous population of normal and pathological subjects were analyzed to establish limits of the acoustic techniques when the data are collected in clinical (noisy) environments with medium-quality tape recorders. The acoustic techniques included glottal inverse filtering for estimation of the glottal volume velocity waveform and residue inverse filtering for estimation of the glottal source function. The principle effort has been directed at establishing the procedures for the data collection, including an extensive programming effort on mini-computers. Based on the availability of these machines, it was decided to directly digitize and analyze all of the vowel data in an on-line interactive manner, thus providing immediate results to the research staff. It was felt that the development work for this on-line procedure is warranted because of the projected large number of subjects.

A method for estimating the glottal source waveform by having a subject phonate into a long anechoically-terminated tube was used in studies of normal and pathological voice production by a NINCDS investigator. Data from reflectionless tube studies have appeared in several publications. However, the accuracy of this method has practical and theoretical limitations which have not been fully explored. In order to provide an accurate estimate of the source waveform, several conditions must be met. The tube itself must be as nearly as possible reflectionless, and well matched to the cross sectional area of the vocal tract. Additionally, the vocal

tract itself must have a nearly uniform area function, and must not contain side resonators, but the effect of departures from these conditions have not previously been studied. An articulatory synthesizer has been implemented. The simulation model was modified so that its oral tract was anechoically terminated at the lips, and oral output was calculated. Effects on the accuracy of the reflectionless tube method was quantified under the following conditions: (1) The ideal, uniform vocal-tract condition, (2) a more realistic "neutral" vocal tract, appropriate for a schwa vowel, (3) the introduction of a nasal leak in the neutral vocal tract configuration, and (4) non-neutral vocal tract configuration. Performance of the method was found to degrade seriously under the last two conditions.

Communicative Aids

A NINCDS investigator reports the implantation of a human subject with a multichannel electrode into the scala tympani. Although testing is very preliminary, initial results indicate that all eight channels are working. The subject can appropriately rank electrodes by the apparent pitch, and can discriminate some speech when the array is driven by the coded output of a frequency spectrum vocoder. Psychophysical studies should resolve further important questions regarding electrode array design and function that are relevant to increasing safety of these devices and to potential simplification and increased sophistication of the electrode driving electronics.

Additional studies are in progress to address the following problem areas associated with cochlear implants. What are the exact conditions of charge and current density at which damage to the auditory nerve occurs in animals? What stimulation patterns and levels can be tolerated? How do multielectrode arrays code sound sensation for implanted patients? What excitation patterns of the surviving nerve fibers in man can be evoked by or stimulated by complex multielectrode arrays? What are the optimal speech processing options available in this work? How do these neuro-prosthetic devices compare with carefully fitted hearing aids in patients undergoing the same intensive aural rehabilitation training? What is the stability of the improvement from use of a cochlear implant and what is the status of the auditory nerve in patients who have been implanted for a considerable period of time?

Studies of other prosthetic devices for the hearing-impaired include one of the multipoint electrotactile speech aid (MESA) to evaluate the transmission of connected discourse to the skin. The identification of vowels and consonants were evaluated under three receptive conditions: 1) Tactual; 2) lipreading; 3) combined tactual and lipreading. The results using artificially deafened normal-hearing adults for absolute vowel identification were as follows: 95 percent correct, tactual alone; 90 percent correct, visual alone; 98 percent correct, tactual plus visual. For absolute consonant identification these subjects achieved 45 percent correct, tactual alone; 40 percent correct, visual alone; 98 percent correct, tactual plus visual. The voicing feature was supplied by the MESA and place of articulation information was supplied by lipreading.

A NINCDS study was completed on hearing aids for patients with profound hearing loss. Hearing aids were recommended for 10 of the 18 subjects. Of those subjects who were aided, the median speech detection level was 45 dB with a range of 35 to 60 dB. A series of 22 additional subjects were seen for hearing aid evaluations. Seventeen Ss were fitted, 12 monaural fittings and 5 binaural. Directional microphones were generally unsatisfactory because they reduced too drastically the beneficial environmental cues; on the other hand, the front-facing microphone was subjectively rated as a positive factor by most subjects. Compression amplification aids were obtained in slightly less than half the cases; input compression was consistently superior to output compression. A battery of speech reception tests is necessary because not all subjects can perform at the same level and no one test has emerged as the best predictor of hearing aid performance. Although most of the subjects have experienced episodic or constant tinnitus, this has not emerged as a major problem. A few have complained that tinnitus detrimentally affects hearing aid use at times and only one has reported relief of tinnitus as a result of hearing aid use.

A NINCDS investigator selected subjects (Ss) considered to have sensorineural hearing impairment close to symmetrical in both ears. Five of the ten evaluated Ss have hearing levels better than 30 dB at frequencies below 1000 Hz. Above this frequency, the loss increased at a rate up to 40 dB per octave. All Ss were evaluated audiometrically before final selection. The following tests were performed: Pure-tone, air- and bone-conduction thresholds; air-conduction thresholds by third-octave noises; most comfortable levels and uncomfortable levels for third-octave noises, as well as speech signals (recorded discourse); speech reception thresholds; speech discrimination scores; tone decay; tympanometry; and reflex decay. A questionnaire was completed by each subject in order to assess his everyday environment and hearing aid satisfaction. Speech tests in noise and under various amounts of compression were administered to all subjects. The no-compression condition was more deleterious to speech recognition than the compression conditions. These results indicate that the speech intelligibility improves with compression and time constant values are not critical if their magnitudes are below 10/90 ms.

NINCDS supported a study of localization testing and binaural hearing aid amplification. The findings indicated that localization of phantom images produced by two sounds coming from two loudspeakers with a controlled level difference between them can be used as a method for assessing localization abilities in sound field. The method is almost as accurate as localization of real sources and can be used when subjects listen through hearing aids. When binaural hearing aids are introduced with a 10 dB difference in gain setting, significant shifts in localization have been found to occur. Subjects with bilaterally symmetrical thresholds generally localize normally. Older subjects tend to produce greater variability of adjustments. In the aided condition some subjects localized normally when the gain settings of the aids were equal and produced shifts in localization with unbalanced hearing aid gain settings. However, some patients localize incorrectly in the aided condition regardless of the gain settings. For these subjects slight differences in positioning of the earmolds caused modification of the sound field in the ear canals and prevented normal localization.

Language

NINCDS supports studies concerned with the structure and acquisition of a language in another mode--the visual-generated language used by the deaf. As a way of examining the biological foundations of language, investigators use an "experiment of nature" in which hearing is not present from birth. They study the development of a language which uses the visible hands and body instead of the essentially hidden vocal apparatus and which relies on the eye for analysis instead of the ear. The investigators examine the relationship of speech and language--namely, what would language be like without speech? What properties of the complex phenomenon we call language are due to the mode, due to the channel in which the abstract entities are realized, and what properties are due to more general linguistic and cognitive faculties? What is the effect of the language developed for vision instead? In this sense the studies are directed toward investigating the universal properties of language.

NINCDS investigators have found that American Sign Language is a heavily inflected language with inflection being the form of grammatical patterning. It differs from English in the degree to which it makes use of inflectional devices. Inflections are used to change person reference for verbs; reciprocal inflections indicate mutual relation or action; inflections provide number (two, three, many); others indicate distributional aspect (to each, to certain ones, to unspecified recipients in distributed actions); these are inflections for temporal aspects (often, regularly, continuously, continually, characteristically, incessantly); and inflections provide manner and degree (with ease, readily excessively, approximately, a little). Since the form of these morphological inflections differ between sign and spoken languages, the mode in which the language develops may make a crucial difference. Under different inflectional patterns, a sign can be built up in a multitude of ways to create a complex single unit which compacts a great deal of information simultaneously.

A NINCDS research project explores the characteristics of a right hemisphere mechanism for reading, specifically: (1) Whether left hemisphere damaged patients with the syndrome of "phonemic dyslexia" are relying on a right hemisphere reading mechanism, and (2) whether right hemisphere reading capacities in normal subjects show the characteristic features of reading performance in phonemic dyslexia. The principal experiments involve split-field studies of phonemic dyslexics and normal subjects--to determine the word recognition capabilities in the two visual fields of patients and whether the two visual fields show different patterns of word recognition across lexical categories in the normal subjects.

The speech perception capabilities of aphasics, right-brain-injured and control subjects were compared in a study of discrimination and labelling of synthetic stop consonants as formant transitions are lengthened to 45, 65 and 85 msec. Enhanced discrimination was obtained at 65 msec, but labelling was not affected in the aphasic subjects. Non-speech control stimuli did not show these effects. Further, Broca's and Wernicke's aphasics

were required to make auditory-auditory and auditory-pictorial same-different judgments and picture selections involving close phonemic discriminations. Results indicated that the comprehension defects of Wernicke's aphasics are primarily semantically based. Another study assessed the naming ability of aphasics in relation to semantic organization. Deficits in semantic field were most notable in Wernicke's and anomie aphasics, but non-aphasic right-brain-injured subjects were also deficient in this regard. The reaction time component for decoding meaning is shorter in Broca's aphasics than in Wernicke's. Further, for Broca's aphasics, the time for decoding meaning is independent of variations in time for search and identification, while for Wernicke's aphasics the two components are correlated. Analyses of thematic structure, syntactic complexity and vocabulary usage by aphasics and normals in retelling a series of picture stories reveals differences between fluent, non-fluent and control subjects at the organizational as well as speech production levels of discourse.

Other NINCDS supported aphasia studies focused on variables involved in comprehension in aphasia. One study used a sentence-picture matching task. The study examined aphasic comprehension for a large number of sentence constructions: Active declarative, passive, subject and object cleft, and pseudo-cleft sentences. Further, the sentences were either semantically constrained, semantically improbable, or semantically anomalous. Broca's aphasics were able to take advantage of the semantic constraints, whatever the sentence type. Wernicke's aphasics, however, were blocked on the application of a semantic strategy. A second study focused on memory factors in sentence comprehension. Specifically, a probe paradigm was used to assess memory for the surface structure of sentences in Broca's and Wernicke's aphasics. Three types of sentences were used: Active, passive, and center-embedded sentences. Results showed that for both patient groups memory for function words was especially impaired relative to the patients' abilities to recover content words. Further, both groups had marked difficulties in remembering center-embedded sentences. A second experiment ruled out the possibility that this latter result was due to the greater syntactic complexity of the center-embedded sentences. The results of these experiments indicated that fluent Wernicke's aphasics as well as Broca's aphasics cannot build normal sentence structure memory representations.

Broca's and Wernicke's aphasics were also assessed on their memory for words. A recognition task was used whereby on any one trial, some words were instances of the same superordinate category having a common abstract conceptual feature. Recognition clusters were examined for either superordinate conceptual links and compared with data obtained from neurologically intact patients. The data suggest that verbal memory limitations in aphasia can only partly be accounted for by reduction in conceptual features structuring lexical knowledge. These data raise the possibility that aphasics may have a disturbance of mnemonic processing quite apart from any disruption to language.

Speech

NINCDS has supported studies in speech motor control in normal adults to develop a more sophisticated understanding of normal speech physiology, with particular emphasis upon (1) measures that are applicable to the observation of speakers with neurological impairments and (2) features of speech production that reflect, most directly, underlying motor neurophysiology. Due to the complexity of peripheral speech physiology and the need to quantitatively distinguish between contributions of central and peripheral mechanisms, these studies were conducted using a systems engineering approach. The major developments were (a) a quantitative model of the speech aerodynamic system, with which to interpret and refine our measures in normal and neurologically impaired speakers, (b) mathematical analysis routines for determining the mechanical and physiological ranges of various speech system variables (e.g., pressure, flow rate, movement, (EMG) in normal and neurologically impaired speakers, and (c) the analysis of potential problems in using linear systems approaches for determining the transfer function characteristics of active speech tissue.

Other studies were concerned with the role of afferent feedback in the control of speech gestures and articulatory coordination including studies of (a) unanticipated disturbances (interruptions in auditory feedback and dynamic or steady state articulatory position perturbations were introduced), (b) motor equivalence with regard to changes in phonetic context and between two synergistic muscles acting upon the same speech structure, and (c) coordination patterns between the tongue and jaw.

Acoustic studies of normal adult speech were carried out to investigate (1) developmental changes in vowel formant frequencies in a task of imitation with computer-synthesized vowels as stimuli, and (2) developmental changes in segment durations in a task of sentence recitation. From the data on vowel formant frequencies, it was possible to construct isovowel lines in the F_1 - F_2 and F_2 - F_3 planes. These lines are linear approximations to the group formant-frequency data and appear to have utility in describing the relationship between formant frequencies during speech development and in evaluating vowel formant structure in various speech disorders. The investigation of segment durations revealed that with maturation, both the mean segment duration and the intraindividual variability of segment duration decrease. Adultlike means and variabilities are achieved by children aged about 12 years, in agreement with previous research on speech production in children. However, the data indicate that the effect of age on control of segment durations is complex, in that some segments are more affected by age than are others. Apparently, there is an interaction of age with motor-phonetic characteristics of speech production. The data are expected to be useful in the study of neuromotor disorders of speech, especially those affecting children. Physiological studies are now underway to explore how maturation affects physiological variables such as intraoral air pressure and electromyographic recordings from the lips. The combined acoustic and physiological research has been useful in describing the process of speech development and in the development of quantitative methods for the study of the dysarthrias. As an example of the latter, data obtained in a study of normal speech maturation have been helpful in evaluating the speech patterns in the dysarthria associated with cerebellar disease.

Research in the area of articulatory organization focused on acoustic, electromyographic, and cinefluorographic studies of segmental and supra-segmental coarticulatory phenomena. One line of experimentation was concerned with the nature and extent of both anticipatory and carryover coarticulation. The literature suggests substantial coarticulatory effects on a speech gesture from at least the two or so segments immediately preceding and following it. Studies at the acoustic, movement, and electromyographic levels further suggest that while there is extensive temporal layering among gestures associated with immediately adjacent segments, effects extending over two or more segments are less common than the literature reports. Furthermore, although anticipatory effects have attracted far more attention in the literature, carryover effects appear to be larger in magnitude and more prevalent.

In studies of velopharyngeal function, EMG recordings were made from the levator palatini, superior and middle pharyngeal constrictors, palatopharyngeus, and palatoglossus muscles in three speakers of American English for a number of different phonetic contrasts, oral and nasal consonant segments, voiceless and voiced stop consonants, open and closed vowels, and front and back vowels. The levator palatini is the primary muscle for velopharyngeal closure, and a description of the effect of phonetic environment on its function was determined. The other muscles work synergistically with the levator palatini. While this holds for the palatopharyngeus muscle, its contraction is strongly affected by phonetic environment--specifically, the palatopharyngeus is active for oral phonetic segments, and is more active for consonant than for vowel segments; it is, however, very much more active for open than for closed vowels, apparently acting to narrow the faucial isthmus for these vowel articulations. No other muscle studied had a pattern of activity that resembled that of the levator palatini--the superior and middle constrictors were most active for low levels in one speaker, but were essentially inactive for the two remaining speakers. The palatoglossus muscle was active for back vowels and velar consonants, indicating that it is involved in tongue-body movements and, like the palatopharyngeus, in faucial isthmus narrowing.

One NINCDS study was designed to assess the ability of children with a limited functional articulation disorder--the substitution of /t/ or /d/ for /s/--to identify the sounds they articulate correctly and incorrectly. Previous research which used natural speech signals in discrimination tasks with heterogeneous groups of articulation disordered children has not led to a consistent picture of the relationship between deviant articulation and phonetic perception. An attempt was made to determine whether children who substituted /d/ or /t/ for /s/ made more errors on an /s/ to /t/ identification task (a task involving the sound they did not produce) than on a /t/ to /d/ identification task (a task involving sounds they did produce), and to determine when /s/ was identified whether the phoneme boundary between /s/ and /t/ (the point of 50 percent /t/ and /s/ responses) fell at a different location for the articulation disordered children than for the normal children. That is to say, would the children who did not produce /s/ need more /s/-friction to identify a stimulus as /s/. Most children who substitute /t/ or /d/ for /s/ do not evidence errors in the identification of /s/. However, some children (indeed 50 percent in the first sample) do

make errors in /s/ identification, but do not make errors in /d/ or /t/ identification. The results led to the following conclusions: (1) At least some children who substitute /t/ or /d/ for /s/ do not identify stimuli initiated by /s/ in a normal manner, (2) the abnormality in identification performance may be limited to the misarticulated phone, (3) the abnormality in identification is most readily evidenced when the stimuli are synthetic speech (rather than natural speech) and (4) at one stage of perceptual development children who substitute a stop for /s/ evidence a restricted internal representation of /s/.

Some of the children who substitute a stop for /s/ were frequently found not to actively attend to the task at hand, making errors on /s/ but not on /t/ or /d/. When they are encouraged to attend to the task, they identified the stimuli in a normal manner. Thus, these children do not appear to have "perceptual" problems. Rather, they make errors in /s/ identification because they are not attending and not because they can not discriminate. These results indicate that few children have "perceptual" problems with /s/. Thus, discrimination training for the majority of children with functional disorders of articulation of /s/ would seem to be of little value.

A NINCDS study seeks to specify the nature of laryngeal behavior associated with instances of stuttering as well as the (dis)similarity between these laryngeal behaviors and those associated with fluent speech productions. The purpose is to develop a detailed and comprehensive description of the laryngeal associates of stuttering so that evaluation/theorization regarding the relative significance of laryngeal behavior to onset (origins) and moment (instances) of stuttering can be made on the basis of empirical evidence. A major goal was to collect data regarding laryngeal behavior during instances of stuttering and to distinguish observable (viewable) from non-observable (non-viewable) laryngeal behavior associated with stuttering. A secondary goal was to temporally segment the precise beginnings and endings of each instance of stuttering such that laryngeal behavior videotaped through means of the flexible fiberoptic naso-endoscope (fiberscope) during the time course (duration) of each stuttering can be subsequently assessed (on a videoframe-by-videoframe basis). The major goal has been accomplished. The number and duration of instances of stuttering as well as a distinction between those stutterings which are associated with observable versus non-observable laryngeal behavior have been studied. Determining observable from non-observable laryngeal behavior requires a videoframe-by-videoframe assessment of laryngeal behavior. All laryngeal behavior was videotaped at 30 frames per second and each of 380 instances of stuttering identified. Samples had mean durations of 1.05 seconds yielding approximately 32 videoframes per stuttering. Temporally segmenting the beginnings and endings of each stuttering was accomplished using time-coded (hours, minutes, seconds and frames) recorded onto the videotape along with the fiberoptic image of the larynx. This procedure provides a very precise temporal correlation between the acoustic realization of the stuttering (as analyzed by sound spectrography) and visual realization of the laryngeal behavior associated with that stuttering (as seen on the television monitor). Thus, the audio and video beginnings and endings of each stuttering event can be temporarily aligned and measured in a precise, accurate fashion.

Touch

A NINCDS investigator completed a series of experiments comparing two modes of vibrotactile pattern presentation. The patterns were presented to the fingertip via the Optacon display and were generated using the PDP 11/34 computer. One mode of presentation, the scanned mode, moved the letter to be identified across the tactile array in the manner in which the Optacon is ordinarily used. The second mode of presentation, the static mode, generated the tactile pattern by turning all the elements on in the pattern simultaneously. The static mode proved superior to the scanned mode at all durations less than 200 msec. Good letter recognition was possible in the static mode at durations as short as 4 msec. Performance in both modes decreased as pattern duration decreased, but it was shown that, in the case of the static mode, this decrease was probably the result of decreasing the perceived intensity of the pattern as its duration decreased. Both modes were also subjected to forward and backward masking. Both modes showed similar masking functions, a backward masker producing more interference in letter recognition than a forward masker.

In other experiments using the computer controlled static mode of presentation, pairs of patterns were presented to the fingertip, one member of the pair to the upper portion of the fingertip and one member to the lower portion. The observer's task was to say whether the two patterns were the "same" or "different." The time between the presentation of the first pattern and the second pattern was varied in an attempt to measure the limits of what might be termed "tactile short-term sensory store." The results using simple patterns, vertical lines, showed a decrease in correct discrimination as the interstimulus interval (ISI) was increased from 0 to 50 msec. As the ISI was increased beyond 50 msec, performance began to improve once again. The observers seem to be attempting, with decreasing success, to integrate the two patterns into a single perceptual unit as ISI increased to 50 msec. Improvement at ISI's greater than 50 msec may indicate successive processing of two inputs as attention is shifted from the top to the bottom portion of the fingertip.

One NINCDS investigator is exploring chronic pain and hyperpathia. Touch detection thresholds and mechanical pain thresholds were measured by means of mechanical pulses delivered through a vibrator and by a standard set of von Frey hairs. Displacement amplitude of the vibrator was monitored by a capacitance meter. The difference in resting skin temperature, measured prior to testing, between the normal and abnormal sides was statistically not significant. This contraindicates a sympathetic reflex dysfunction at the times when the examinations were made. In the total group the abnormal side was significantly less sensitive than the normal side with respect to the detection of warm and cold stimuli. The difference between the warmth and cold detection thresholds (temperature difference limen) has been shown to be expanded in some cases of peripheral neural pathology. This index was significantly larger on the abnormal side as compared to the normal side. The total group showed no significant differences between normal and abnormal sides on measurements of heat pain, cold pain, or heat-pain tolerance thresholds. However, closer inspection of the data revealed two

distinct subgroups with respect to thermal pain; one hypersensitive and the other hyposensitive to thermal pain. The groups were not different on their normal sides, nor could they be distinguished by any measurement other than thermal pain. Detection thresholds for mechanical pulses were significantly higher on the abnormal sides of patients and reaction times to pulses were longer. Detection thresholds to von Frey stimulation were also higher on the abnormal side, but the differences were not marked. Pain produced by mechanical pulses and von Frey hairs was clearly lower on the abnormal side since pain could not be produced on the normal side of any patient by either of these methods. The hypo- and hyper-sensitive groups (thermal pain) could not be distinguished by any of the mechanical-stimulus testing.

One NINCDS supported study has shown that the palmar skin of the human fingertips performs a function of an efficient sense organ with high sensitivity and discrimination. Therefore, knowledge of the composition of its sensory receptors, their exact morphology and microtopography is essential in understanding the functions of this cutaneous area. It has become apparent that the free endings of the hairless digital skin differ from those of the hairy skin in two important ways. While each penicillate ending of the hairy skin has horizontal plexiform distribution over a substantial skin area which overlaps that of the adjacent penicilli, the free digital endings have "punctate" distribution. Moreover, while the penicillate endings of the hairy skin are poor in morphologically distinct axoplasmic organelles, the digital papillary endings are packed with organelles, microvesicles and glycogen granules resembling morphologically the axon terminals in hairs and Meissner corpuscles. The above findings may signify that the free digital endings are highly active metabolically and are slowly adapting receptor organs. Consequently, they are well designed for precise localization of a stimulus and for two point discrimination. Such information may be useful when electrophysiological and psychosomatic experiments are designed and the results are analyzed.

Taste

One NINCDS investigator seeks insights into physiochemical processes attending the interaction of tastants with taste receptor membranes by surface chemical studies of the effects of salts and acid on the surface pressure of phospholipid monolayers. Earlier studies have suggested that phospholipids may play a role as receptor groups for salt and acid in taste reception. Changes in surface pressure with tastant concentration may be important in the transduction process. In one study the phospholipid monolayer is spread on a salt solution at constant composition and pH. In the second study, the phospholipid is spread over one salt solution, then rapidly transferred to another. In the first case, the salt concentration is fixed, whereas in the second it must diffuse to the surface before establishing equilibrium. The latter method, though technically more difficult, gives insight into the time course of the approach of a tastant to the receptor surface. Both methods show that the response of the surface pressure to changes in salt concentration is generally nonmonotonic. The implications are important in providing a rationale for both salt and dilution or "water" responses.

It is known that following adaptation to salt at a given concentration, many species (including man) react behaviorally and electrophysiologically to both salt concentration increases and decreases. The behavioral and electrophysiological response functions are U-shaped with changes in salt concentration. That is, they give responses with increasing deviation from adapting conditions. The deviations may result in either higher or lower final concentration. The change in surface pressure with salt concentrations is similar. At low salt concentration and high salt concentration the surface pressure is low and at some intermediate concentration the surface pressure reaches a maximum. In the case of phosphatidic acid monolayers the maximum occurs at about 0.1 M NaCl.

The purpose of one NINCDS supported study is to analyze responses from higher-order taste relays and to relate these to the activity of lower-order neurons, the coding mechanisms for which have been described. The goals are to study the responses of third-order (pontine) and fourth-order (thalamic) cells as they respond to a series of concentrations of each of the basic taste stimuli. Such intensity studies have been completed by other experimenters for first-order (chorda tympani) and second-order (solitary nucleus) neurons, and a simple logarithmic relationship between concentration and response rate has been established. In the pons, neural responses to basic taste stimuli (NaCl, HCl, sucrose, quinine) are purely excitatory. Log-log plots of stimulus concentration versus response magnitude fall in straight lines with slopes of about .2 for all four chemicals. The shape of the activity envelope across many neurons is thought to represent the taste quality of a chemical. These shapes were virtually unaltered as the activity envelope rose with stimulus intensity, suggesting that the "saltiness" of salt, for example, does not change as the salt becomes more concentrated. In all ways, the pontine results point to a well-defined and orderly processing of taste quality and intensity information. The thalamus appears to present a major change. While responses from brainstem nuclei (that is, the three pre-thalamic links of the synaptic chain) are excitatory and strong to the basic stimuli, thalamic responses are sluggish and unreliable. Many cells respond with inhibition. Temporal characteristics are also difficult to describe. Thalamic taste neurons do not simply process information in the ways predicted by the heretofore successful theories of gustatory neural coding.

One NINCDS supported investigator has reported completing exploratory experiments to measure binding of ^3H -labeled methylated monellin to taste and nontaste tissue preparations. Binding was several-fold greater to bovine circumvallate (taste) preparations than to those derived from tongue epithelium devoid of taste papillae. Also, binding to the circumvallate was displaced by sugars (sucrose and lactose), but binding to the epithelial preparation was not. This evidence suggests that some overlap occurs in specificity of the monellin binding sites for other sweet-tasting compounds. Binding of ^3H -monellin was also measured to human taste tissue preparations provided at autopsy. These results showed also that binding to the circumvallate preparation was significantly greater than that to the epithelium. In addition, some competition between other sweeteners and monellin binding occurred. These results help to establish binding as the initial recognition step in taste. Plasma membranes were isolated from

catfish taste tissue Fraction P2 and characterized. Binding activity for L-³[H] alanine was localized to the plasma membrane, demonstrating that the receptor sites are located in these membranes at the external surface of the cells. Other exploratory experiments have been carried out in order to establish an immunological approach to characterize taste receptors. Antibody techniques have been established in order to ultimately produce an antibody against the receptor preparation and could then be used in studies of specificity of the binding sites.

Smell

One NINCDS investigator has initiated a physiological analysis of the olfactory projections. Single unit recordings were made from mitral/tufted cells during antidromic stimulation with electrodes on the surface of the olfactory cortex and olfactory tubercle. In preliminary results, 36 cells have been tested for driving by olfactory tubercle and cortical electrodes. Sixty-nine per cent were driven antidromically by both tubercle stimulation and one of a set of six cortical electrodes. Many mitral or tufted cells projecting to the cortex may send a collateral to the olfactory tubercle. There is a possibility that in many of these cases there was current spread from the tubercle stimulating electrode to the lateral olfactory tract therefore producing an artificially high estimate of collaterals. Future experiments will be required to estimate the degree of current spread and to demonstrate the presence of collaterals by determining the times required for collision of action potentials elicited by separate sites.

Several odorants were compared by a NINCDS supported investigator in the dog olfactory nerve twig recording preparation. Amyl acetate elicited the largest response and was used as the standard for comparison. The response dependence on nasal flow rate was least for amyl acetate, responses tending to reach concentration-dependent plateaus at the limit of 100 cc/sec. Response-concentration curves, at 32 cc/sec, ranged highest to lowest in the order amyl acetate, anisole, butyric acid, dimethylbenzylcarbonyl acetate (DMBCA), linoleic a., myristic a. and oleic a. The magnitude of response to DMBCA was small, although in turtles the maximal values for amyl acetate and DMBCA are about equal. The butyric a. response relative to the amyl acetate response was noticeably greater than in turtle and rabbit. However, responses to the large fatty acid molecules were small. The butyric a. response dependence on flow rate was so strong that the response was approaching that to amyl acetate at 100 cc/sec. The use of butyric a. caused responses to other stimuli to increase, an effect interpreted as due to increase in accessibility to the olfactory receptors caused by reflex changes in nasal dimensions.

A NINCDS investigator has isolated a specific marker protein for olfactory receptor cells from both mouse and rat tissues and used it to prepare an antibody. This marker protein is synthesized by receptor cells and transported by axoplasmic flow to the olfactory bulb. An immunohistological study of the localization of the olfactory marker protein in adult and developing rats and mice was begun. The technique for localization of the marker protein in tissue was the indirect immunohistological technique using peroxidase-anti peroxidase conjugated

antibodies. In adult mice and rats the reaction product indicating the presence of marker protein is present in the outermost fibrous layer of the olfactory bulb. From this layer, branches enter the glomeruli and arborize into the outer half to two-thirds of each glomerulus. In adult rats and mice the marker protein is found in heaviest concentration 1) in axon bundles in the lamina propria of the olfactory mucosa and 2) in perikaryon regions of the olfactory receptor cells. Basal cells, supporting cells and the deepest layers of olfactory receptor cells are negative.

The possibility of laterality in the olfactory system is being studied with NINCDS support. It was noted that left and right handed subjects appeared to differ in their nostril of greater sensitivity. To pursue this observation the thresholds of both nostrils to n-butanol in nine left-handed and ten right-handed subjects using a two-interval forced choice paradigm and a flow dilution olfactormeter were compared. Anterior rhinoscopy was carried out on all subjects by an otorhinolaryngologist to determine the patency of each subject's airways. The left and right-handed subjects differed significantly in their side of greater sensitivity ($P < .02$) with the left-handed subjects consistently showing greater sensitivity on the left side of the nose and the right-handed subjects showing a tendency, though weaker, towards the right. Whether these differences are related to "brain dominance" per se or whether they are due to some subtle maneuver such as unwittingly sniffing with a greater volume or greater flow rate through the "preferred side" is currently under consideration. Even if this latter were the case rather than "brain dominance" per se, these studies would still contribute to a better understanding of how humans investigate their odorous environment. This relation between nasal side sensitivity and handedness might have been stronger if there had not also been an independent effect due to airway patency, i.e., an inverse relationship between degree of patency and sensitivity. An inverse relationship is not inconceivable since constrictions in the nasal passageways (short of complete obstruction) could possibly force more odorized air into olfactory cleft at higher flow rates and with increased turbulence. In cooperation with the Radiology and ENT Departments the investigator has been visualizing the flow of ¹³³xenon-laden air through human cadaver noses. This technique looks promising for determining the flow characteristics of air passing through different parts of the nose under differing inspiratory strategies and differing degrees of patency, thus describing for the human being those factors controlling the access of odorized air to the olfactory cleft.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

VETERANS ADMINISTRATION HOSPITAL, MINNEAPOLIS, MINNESOTA (Y01-NS-4-0019)

Title: Development of a Research Tool Concerning Speech
and Language Therapy for Aphasic Adults

Contractor's Project Director: Robert H. Brookshire, Ph.D.

Current Annual Level of Support: \$0

Objectives: To develop descriptive and quantifiable systems for coding the content of speech and language treatment sessions with aphasic adults. Coding results will differentiate between various types of therapeutic approaches on the basis of differences in treatment content. The system is needed as a tool for conducting research contrasting the efficacy of various therapeutic approaches for the treatment of aphasia.

Major Findings: Two methods of coding the content of aphasia therapy called Clinical Interaction Analysis System (CIAS) have been developed and demonstrated to be both valid and reliable in a field evaluation study involving six supervised training sites. Coder training manuals were demonstrated to be adequate for supervised and unsupervised training of both experienced and inexperienced speech pathologists using either the long 39 item coding form or the short 26 item form. The final revisions and printing of the CIAS training manuals have been completed for distribution to investigators. The more complete 39 item system is used with videotaped recordings of aphasia treatments while the 26 item system can be used to obtain a valid and reliable representation of the content of an ongoing treatment session.

During the last year, two journal articles have been published; one describing the long system and the other reporting on valid treatment sampling techniques. Several presentations have been made at scientific meetings.

Over 20 different 30-minute videotaped treatment sessions obtained from different clinical settings were coded and submitted to a content analyses used in the completion of two investigations. One study examined the effects of feedback and explanation on improving patients language performance during therapy; neither were found to be helpful although modeling was. In the other, a subjective rating scale was developed to gather information on clinician, patient and treatment session characteristics. Eleven categories were found to have adequate reliability and were used in subsequent analyses contrasting the effectiveness of various types of treatment. Both these studies are presently being prepared for publication.

Significance to NINCDS Program and Biomedical Research: This coding system provides a badly needed research tool. It quantifies the differences in content of various treatment approaches and has been used already to demonstrate what clinician behaviors are most beneficial to aphasic patients.

The final printed manuals and coding forms have been supplied to the Veterans Administration Cooperative Study Center--VA Co-op Study on the Effects of Treatment on Recovery From Aphasia. Study Center personnel have learned to record treatment sessions using the CIAS short system. The CIAS will be used in this nationally based study to verify and describe the content of clinic-based and home-based treatment. Thus, the coding system is already being used for the purpose for which it was developed; in investigations of the efficacy of different approaches for aphasic adults.

Proposed Course of Contract: The contract will terminate in August 1979.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

UNIVERSITY OF FLORIDA (N01-NS-5-2313)

Title: Study of Auditory Sensitivity in Young Children

Contractor's Project Director: Donald C. Teas, Ph.D.

Current Annual Level of Support : \$115,889

Objectives: This contract was awarded to study auditory sensitivity in young children. The goal is the development and evaluation of a battery of tests which can be used to characterize the hearing ability of young children not suspected of having hearing deficits and to examine the feasibility of using such a battery to assess the hearing of infants and young children who are suspected of, or at-risk, for hearing dysfunction. Particular emphasis is being placed on the developmental aspects of the hearing ability of this population.

Major Findings: Three measures (auditory brain responses (ABR), blink-inhibition by acoustic leadtones, and behavioral measures of threshold) are being evaluated with infants, young children and adults. Results show that these measures can be confidently employed to assess auditory sensitivity in the target population of 0-3 year old children. ABRs are evoked by filtered clicks centered at conventional audiometric test frequencies and the behavioral responses are measured by two alternative forced-choice tracking procedures with both puretones and filtered clicks. The blink-reflex is inhibited by a leadtone preceding the reflex-eliciting stimulus. Threshold measures in children are within 5-10 dB of those in adults and latencies of ABRs match adult latencies at low frequencies but lag in infants in the higher frequencies. Blink-inhibition data are different from those obtained from adults but the intensity of the leadtone appears to be a critical variable for both groups of subjects.

Significance to NINCDS Program and Biomedical Research: Procedures are needed for assessing the hearing of young children who are incapable of providing conventional responses. Without a battery of tests to assess hearing sensitivity at different developmental stages, evaluation of degree of impairment followed by treatment for this population is not possible at the present time.

Cooperating Units: None

Proposed Course of Contract: With completion of the development of measures of auditory sensitivity, the contractor is collecting data for both cross-sectional and longitudinal studies of the target population. A Technical Merit Review of this contract was performed in July 1978, at which time it was renewed for three additional years of data acquisition and analyses.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

UNIVERSITY OF PITTSBURGH (N01-NS-5-2317)

Title: Study of Estimators of Aphasic Patients' Communicative Performance in Daily Life

Contractor's Project Director: Audrey L. Holland, Ph.D.

Current Annual Level of Support: \$0

Objectives: Conduct a field evaluation study using the test of Communicative Ability in Daily Living to determine the range of communicative abilities among normal adults between the ages of 40 and 80; and, the effects of the following factors on communicative adequacy of adults with:

- Wernicke's aphasia, Broca's aphasia, mixed aphasia and Global aphasia,
- moderate to severe hearing loss acquired after 20 years of age,
- moderate mental retardation since childhood,
- institutional living environment,
- aging (between 40 and 80 years), and
- educational level, sex and occupation.

Major Findings: The study of communicative ability in normal and aphasic aging adults demonstrated that:

- 1) Aging and institutionalization both were associated with greater impairments in communicative abilities in aphasic adults.
- 2) Patients with various aphasic syndromes had different degrees of impairment in communicative ability. Global aphasics were the most impaired followed by transcortical sensory types. Anomic aphasics are least impaired and were superior to mixed types, while Broca's aphasics were somewhat better able to communicate than Wernicke's aphasics.
- 3) In the normal population, older adults are significantly lower in their communicative abilities and institutionalized adults were impaired in their communicative abilities in contrast with non-institutionalized normal adults of the same age.
- 4) Within the normal aging population, females were superior to males in communicative ability.

The field evaluation study also included a group of gainfully employed mentally retarded adults and a group of hearing impaired adults who were successful hearing aid users. The mentally retarded adults were significantly impaired in their communicative ability and scored within the aphasic range. An extremely high relationship was found between IQ level and communicative ability in the mentally retarded subjects. In addition, their communicative ability was found to be related to their functional independence and work habits. Finally, although the hearing impaired adults were significantly lower than the normal control subjects in communicative ability, only one subject scored outside the normal range in communicative ability.

Significance to NINCDS Program Biomedical Research: A valid measure of degree of handicap of communicatively impaired adults has been developed and found to be useful not only for aphasic patients but cognitively and hearing impaired adults as well. This measure has also been found to be sensitive to intellectual abilities, aging and institutionalization. It differentiates between patients with different aphasic syndromes and identifies their difficulties in communicating. Thus, the objective of the project was met; a valid measure of communicative ability was developed for research with communicatively impaired adults.

Cooperating Units: None

Proposed Course of Contract: The contract was terminated in April 1979 following successful completion of the workscope.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (N01-NS-5-2322)

Title: Measures of Children's Language Performance

Contractor's Project Director: Janice E. Laine, Ph.D.

Current Annual Level of Support \$0

Objectives: The objectives of this project were to:

- a. Develop a set of measures of children's language performance which would be sensitive to small changes in the language performance of neurologically impaired children,
- b. prepare administration and scoring manuals for training speech pathologists to be reliable examiners, and
- c. demonstrate the validity and reliability of the measures for assessing small changes in the language performance of language delayed children.

Major Findings: The Measures of Children's Language Performance (MCLP) was formed of over 500 test items found to be valid and reliable for assessing language performance in language impaired children during the pilot testing phase. The test provides an indepth assessment of language abilities of language impaired children using test items closely matched to their particular level of language development. Nine different language performance subtests provide a comprehensive assessment of language comprehension, expression and speech repetition. Each language system, including semantics, syntax, morphology and phonology is assessed independently.

A field evaluation study of the MCLP was conducted on 70 language impaired children to determine test validity for detecting small changes in language performance of language impaired children following six months of language therapy as well as test-retest reliability. The field evaluation demonstrated that the MCLP had the following characteristics:

- 1) Inter-examiner reliability was adequate on all but the subtest of receptive syntax.
- 2) The MCLP was sensitive to changes in language performance in all language areas, particularly in receptive language.
- 3) The validity of the MCLP was greatest for subtests of language expression when compared with teachers and parents assessments of change in children's performance during the experimental period.
- 4) Validity was greatest for the expressive subtests when related to standardized language assessment measures.

The first stages in the development of a comprehensive language assessment tool has been completed with adequate inter-examiner reliability, internal consistency and validity for assessing the language performance in language impaired children. Further improvements are needed for the subtests assessing language comprehension of syntax, semantics and morphology.

Significance to NINCDS Program and Biomedical Research: This set of language measures will provide a badly needed research tool necessary for doing research on the language development difficulties of language impaired children. This set of measures will be used to study the language acquisition process in language impaired children and to compare the efficacy of various types of treatment for different groups of language impaired children.

Cooperating Units: None

Proposed Course of the Contract: The contract was terminated in December 1978 upon successful completion of the workscope.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

THE JOHN F. KENNEDY INSTITUTE (N01-NS-5-2323)

Title: Study of Sensory and Perceptual Functioning of Young
Children With and Without Delayed Language Development.

Contractor's Project Director: Rachel E. Stark, Ph.D.

Principal Investigator: Paula Tallal, Ph.D.

Current Annual Level of Support: \$47,653 (FY79)

Objectives: To determine how normal, language impaired, reading impaired and speech impaired children differ in their sensory, perceptual and cognitive performance. The study will determine whether any of these groups have distinctive patterns of sensory, perceptual and cognitive functionings, and whether relationships exist between their primary problem in language, speech, or reading on the one hand, and their sensory, perceptual and cognitive functioning on the other.

Major Findings: Although the data analyses are not yet complete, the following results have been reported:

- a) Discriminant function analyses of the sensory, perceptual, cognitive and neurological test data identified five subtests as most important for differentiating between language impaired and normal children:
 - (i) The discrimination between two consonant-vowel syllables when the consonant-vowel transition time is only 40 msec;
 - (ii) a finger identification test on the neurodevelopmental examination;
 - (iii) a visual sequencing subtest for E and K with a 500 msec inter-stimulus interval;
 - (iv) cross auditory-visual stimulus matching; and
 - (v) a visual scanning subtest.

Therefore, deficits in other modalities than the auditory are of importance when differentiating between language impaired and normal children indicating that the difficulties of these children are not confined to the auditory modality.

Additional analyses of the data have demonstrated that those language impaired subjects with speech expression difficulties have corresponding difficulties in auditory perception of speech sounds. Objective methods were developed for quantifying the receptive and expressive language impairments of language impaired children. Also, studies of phonemic constancy

have demonstrated that developmental changes in speech perception occur in normal children between the ages of 4 and 8 and are significantly delayed on language impaired children.

Significance to NINCDS Program and Biomedical Research: Many treatment programs of language impaired children have been based on the assumption that auditory processing difficulties are associated with impaired language development in many children. These research results demonstrate that language impaired children have many other sensory, perceptual and cognitive difficulties in comparison with normal controls. The forthcoming information on the performance characteristics of language, speech and reading impaired children will be critical to improving the diagnosis, assessment and treatment of these children.

Cooperating Units: None

Proposed Course of the Contract: The contractor is in the final stages of data analysis and report writing. The contract will terminate in September 1979 upon successful completion of the workscope.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

WAYNE STATE UNIVERSITY (N01-NS-6-2353)

Title: Evaluation of Procedures for Screening Preschool Children for Signs of Impaired Language Development

Contractor's Project Director: Lynn S. Bliss, Ph.D.

Current Level of Support: \$85,000 (FY'79)

Objectives:

- 1) To develop valid language screening procedures for screening preschool children for signs of impaired language development in English, Black dialect and Spanish.
- 2) To develop reliable instructional materials for training paraprofessionals to administer the language screening procedures.
- 3) To assess the validity and reliability of the selected screening items, when administered by paraprofessionals to English, Black dialect and Spanish speaking preschool children.
- 4) To determine whether language impairments are associated with the occurrence of otitis media and/or mild to moderate hearing loss in preschool children.
- 5) To develop materials for distribution to health and educational service administrators, providing recommendations on how to implement and administer preschool language screening programs.

Major Findings: The contractor is currently completing the field evaluation data collection of hearing screening, language screening and language assessments of Anglo, Black dialect and Spanish speaking children. The Spanish testing is being conducted in Tucson, Arizona, under subcontract. Over 600 children have completed language and hearing screening in the Detroit area; 287 Anglo and 316 Black dialect speakers. Another 200 Spanish speaking children will be assessed in Tucson prior to September 1979.

On the basis of the preliminary results, the numbers of children between two and one-half and four years found to have some delay in language development outside the normal range was between 10 percent and 20 percent with the prevalence significantly greater in Black dialect than Anglo children, and significantly greater in low socioeconomic than middle socioeconomic groups, independent of race or dialect.

The prevalence of middle ear problems and/or mild to moderate hearing loss has ranged between a high of 40% and a low of 20% in different seasons and the two geographic regions.

The preliminary data indicate that the language screening procedures for Anglo, Black dialect and Spanish speaking preschool children can be administered by paraprofessionals who speak the same language and dialect as the children being screened with adequate inter- and intra-examiner reliability.

Significance to NINCDS Program and Biomedical Research: Children impaired in language development cannot progress at the normal rate in school. If such children were detected at preschool age, treatment could begin prior to their entering school. Valid and reliable language screening procedures are needed for conducting early periodic screening for children eligible to receive special assistance under the new Education for the Handicapped Act, 94-142. This project was designed to meet these needs. The results will provide the procedures, examiner training materials and program organization for conducting preschool language screening.

Cooperating Units: University of Arizona, Tucson, Arizona.

Course of Contract: Data analyses of the language and hearing assessment of Anglo and Black dialect children are ongoing while the field evaluation data collection of the Spanish segment of the project will be completed in September 1979. The contract will be terminated in December 1979 upon successful completion of the work and submission of the final report.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

NAVAL RESEARCH LABORATORY (Y01-NS-7-0033)

Title: Feasibility of Use of Acoustic Analysis for Detecting Signs of
Vocal Pathology

Contractor's Project Director: David C. Coulter

Current Annual Level of Support: \$0

Objectives: To determine the potential accuracy of several alternate sensor devices and metric and parametric transformations for the detection of signs of laryngeal pathology. The goal is to determine what equipment and methods have the greatest potential for use in rapid, high-patient-volume screening programs to detect early signs of laryngeal cancer in high risk populations.

Major Findings: Measures of cycle to cycle perturbation, diplophonic signals, and fundamental frequency waver have been developed and applied to acoustic and laryngographic recordings of three groups: Patients with laryngeal neoplasms (carcinoma, nodules, and polyps); nasal ganglia disorders affecting laryngeal control (hypokinesia and dyskinesia); and, normal aging controls. Preliminary analyses indicate the following:

- a) Cycle to cycle perturbations were greatest in neoplastic disease, were present in severe forms of basal ganglia disorders and were noticeable in normal adults who smoke heavily;
- b) diplophonic signals were more frequent and of greater durations in patients with basal ganglia disease and other forms of neuromotor disease;
- c) the amplitude of waver was greatest in patients with basal ganglia disease, other neuromotor disturbances and aging adults; and
- d) a reduction in amplitude and an increase in frequency of waver was associated with laryngeal neoplasms.

Further statistical analyses will be conducted to determine whether any of these measures or other algorithms have high discriminant functions for accurately identifying type of pathology.

Of the sensors evaluated, the laryngograph and accelerometer seem to have equal value for clinical use in the detection and possible assessment of vocal pathology. Although the laryngographic signal is easiest to process, it does not contain information on amplitude variation and the instrument cannot be used with overweight adults.

The final stages of data analysis are ongoing and the project report will contain recommendations for future research and clinical application of these techniques.

Significance to NINCDS Program and Biomedical Research: The prognosis for survival from laryngeal cancer is significantly improved (close to 90 percent survival beyond five years) with early detection. Figures published by the National Cancer Institute indicate that certain portions of the populations are at high risk of developing the disease which can be fatal unless detected in the early stages. The results of this feasibility study are needed to determine the equipment specifications for developing a method of screening for early signs of laryngeal pathology.

Cooperating Units: None.

Proposed Course of the Contract: This interagency agreement will terminate in July 1979, following submission of the final report.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

MINNEAPOLIS MEDICAL RESEARCH FOUNDATION, MINNEAPOLIS, MINNESOTA(N01-NS-7-2378)

Title: A Comprehensive Study of the Language Recovery Process in Adults with Aphasia Following a Cerebrovascular Accident

Contractor's Project Director: Alan B. Rubens, M.D.

Current Annual Level of Support: \$296,000 (FY 79)

Objectives: The purpose of the research is to develop increased understanding of the neurophysiological and behavioral bases of the language recovery process in aphasic adults, during the first six months following a CVA to determine:

- a) The prediction of outcome of aphasia on the basis of the size and location of brain pathology and neurophysiological activity in each hemisphere,
- b) what changes in location and size of brain pathology and neurophysiological activity of either hemisphere, are associated with the degree of language recovery,
- c) what changes in behavior are associated with the degree of recovery from aphasia, and
- d) whether patients' verbal learning/memory deficits are associated with prognosis for recovery from aphasia.

Major Findings: The contractor has been successful in the development and application of the following techniques for the study of aphasic patients: dichotic listening tests; verbal learning and memory assessment; nonverbal cognition and mental reasoning evaluation; language expression and reception tests; tests of auditory discrimination; speech production and reading ability; measures of regional cerebral blood flow during verbal activation and rest; and measures of lateralization of alpha suppression during language listening, block design and resting activities. Also the contractor has successfully developed a method for objective mapping of the size and location of lesions from CT scans.

The longitudinal study of recovery from aphasia during the first six months post onset has begun. At the same time, normal aging adult controls are being examined on experimental test batteries to establish norms for normal aging adults.

A study has recently been completed demonstrating the correspondence between dichotic listening results and the size and location of left hemisphere lesions on CT scans of aphasic patients. The results indicate that when unilateral lesions in the left temporal lobe involve the angular gyrus of the parietal lobe, speech perception is severely disturbed in the right ear on dichotic listening tasks. Thus, dichotic listening results

may provide information on the location of lesions in the left hemispheres of aphasic patients.

Significance to NINCDS Program and Biomedical Research: Language recovery in aphasic adults is not well understood. In most cases recovery is rapid during the first nine weeks following the onset of symptoms. The size and location of brain lesions, regional blood flow, and physiological response of each hemisphere during verbal behavior will be reassessed throughout recovery to determine the association between dominant hemisphere status and level of recovery from aphasia. If recovery is not highly associated with changes in the left hemisphere, and the right hemisphere is found to be involved in verbal functioning, both the right and left hemispheres may be involved in language recovery following a CVA. The results will be useful for determining appropriate approaches for developing effective treatment techniques.

Cooperating Units: University of Minneapolis Medical Center.

Proposed Course of the Contract: During the second phase (3 years), 60 aphasic adults will be studied during the first six months following the onset of aphasia.

During FY 80 , a Technical Merit Review of the contractor's progress will be held as a site visit. The NINCDS will then determine the length of time that subject testing should continue to provide sufficient data for examining each of the hypotheses statistically. Phase II of the research will be completed when these requirements have been met satisfactorily. Six months will then be required for data analysis and report writing.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

UNIVERSITY OF ILLINOIS (N01-NS-7-2380)

Title: Evaluation of a Test of Speech Perception in Noise

Contractor's Project Director: Robert C. Bilger, Ph.D.

Current Annual Level of Support: \$122,440

Objectives: The purpose of this contract is to conduct experimental work to determine the inter-list equivalency, performance by signal-to-babble (S/B) functions, and validity of the Speech Perception in Noise (SPIN) Test.

Major Findings: All ten forms of the SPIN Test have been presented to 128 hearing-impaired listeners at a level calculated to correspond to the loudness equivalent to 60 dB SPL for a normal-hearing listener, and the babble noise was set 8 dB lower. Half of the subjects heard the test through earphones and half via loudspeaker; half were tested in a single session and half in two sessions. Statistical analyses of these results indicated that (a) transducer, (b) visits, and (c) order of testing had no influence on test scores. The average reliability coefficient was 0.906 for the high probability items in a form and 0.848 for the low-probability items. The ten forms tested, however, do not constitute a set of equivalent forms; and it is difficult to identify a subset of equivalent forms, because of the large differences in difficulty among forms with respect to the low-probability sentences.

Significance to NINCDS Program and Biomedical Research: Assessment of supra-threshold speech perception in noise would provide a valuable tool for the practicing clinician in managing hearing-impaired patients. Hopefully, the SPIN Test may also be employed as a predictive measure of the degree of benefit that persons with acquired sensorineural hearing loss may appreciate from a properly selected hearing aid.

Cooperating Units: None

Proposed Course of Contract: Phase I as described above has been completed. The SPIN materials must now be reevaluated to obtain equivalent forms by using the data from 64 subjects in Phase I and cross-validating these data with the remaining 64 subjects. A rearrangement of both speech and babble signals by A/D conversion will be necessary to develop equivalent lists. Phases II and III will follow the completion of this interim work.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

CHILDREN'S HOSPITAL OF PITTSBURGH (N01-NS-8-2384)

Title: Decongestant/Antihistamine Therapy for Otitis Media with Effusion (OME)

Contractor's Project Director: Charles D. Bluestone, M.D.

Current Annual Level of Support: \$110,072

Objectives: To determine if the widely used combination of an antihistamine and decongestant is effective in the treatment of otitis media with effusion.

Major Findings: Nearly 200 subjects have been enrolled in this double blind clinical trial and nearly 150 have completed a four-week trial period. This study began enrolling subjects in August of 1978, and is progressing well. The drug code has not been broken by the clinical team. This assimilation rate is about as expected with the exception of one subgroup and the attrition rate is less than expected. On the initial visit, 52 percent had bilateral OME as determined on the basis of the algorithm for identifying OME. The algorithm is based on otoscopic, tympanometric and acoustic reflex criteria. Another 32 percent had OME unilaterally with the contralateral ear free of effusion, and 16 percent had definite OME unilaterally with an indefinite evaluation of OME on the contralateral side.

Significance to NINCDS Program and Biomedical Research: Otitis media is the most common illness seen in the pediatrician's office and despite the routine use of decongestants and/or antihistamines we lack objective evidence of their effectiveness. Otitis media has been a targeted area of research by NINCDS and this work will provide important information for the treatment of otitis media.

Cooperating Units: None

Proposed Course of Contract: With the rate of subject assimilation as anticipated, the projected number for statistical analysis should be reached and all analysis completed, as planned, in July 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

PRESIDENT AND FELLOWS OF HARVARD COLLEGE, CAMBRIDGE, MASSACHUSETTS
(N01-NS-8-2399)

Title: Laryngeal Carcinoma: Identification of High Risk Factors

Contractor's Project Director: Kenneth J. Rothman, Dr. P.H.

Current Level of Support: \$139,215

Objectives: To identify those individual health, environmental, and occupational factors which will delineate persons at high risk of laryngeal carcinoma in the United States today. The following objectives will be met:

- a. An integration of data available on factors associated with a high risk of laryngeal carcinoma in the United States;
- b. An examination of mortality, incidence data and time trends with significantly high rates of laryngeal cancer over the last 10 years; and
- c. Complete investigations of racial, sex and individual health, familial, environmental, geographic and occupational factors in counties where incidence or mortality is greater than in the general population.

Major Findings: In the first year of the project, the contractor has completed the first objective; an integration of the data available on the epidemiology of laryngeal cancer, and reported the following:

- 1) The age-adjusted incidence for laryngeal cancer in the United states is between 5.9-8.4 per 100,000 per person year.
- 2) Survival for 10-15 years averages 50 percent for laryngeal cancer and incidence in the 60-64 age range for males is between 22.7 and 40.7 per 100,000.
- 3) Incidence and mortality is greater in industrialized areas and highest in Northwest Texas, Coastal South Carolina and Georgia.
- 4) Although incidence has risen slightly in the United States from 6.3 to 7.5 per 100,000 between 1940 and 1970, the rates have doubled since 1940 in Connecticut, New York and Texas.
- 5) There is a strong linear relationship between relative risk of laryngeal cancer and the number of cigarettes smoked per day. Heavy smokers have a relative risk of laryngeal cancer 30 times greater in contrast with non-smokers.

- 6) Heavy consumption of alcohol increases the relative risk of laryngeal cancer by a factor of six when smoking is controlled.
- 7) Occupational factors have not been well studied independent of smoking and alcohol consumption, except for asbestos which can be considered a strong risk factor. Other occupational exposures needing further study include wood dust, nickel, mustard gas, grease and oil, isopropyl alcohol, leather, paper, chemical and textiles.

Significance to NINCDS Program and Biomedical Research: The chances of survival following laryngeal carcinoma can be significantly enhanced with early treatment and the vocal mechanism may be spared when surgical intervention is not necessary. Screening programs are needed of persons at high risk of laryngeal cancer (such as industrial male workers who are heavy smokers and drinkers between 60 and 65 years of age). Before such programs can be initiated, a clearer understanding is needed of what factors could delineate persons at high risk for this disease. The final report of this project will indicate what further research is needed for delineating persons who are at high risk as well as what is currently known about the relative risk for this disease in various sections of the population.

Cooperating Units: The National Cancer Institute, Office of Biometry, and four Richmond County, Georgia hospitals (Georgia Regional Hospital, Medical College of Georgia Hospital, St. Joseph Hospital and University Hospital) will cooperate in a case-control study during Phase III.

Proposed Course of the Contract. Phase I of the research will be complete in June 1979 and both Phase II and III will be initiated upon review of the plans for these two phases by the Project Officer. The contract is scheduled to terminate in two years time in May 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, NORTH CAROLINA (N01-NS-79-2305)

Title: The Acquisition of Language and Communicative Skills by Speech and Sign in Infantile Autism

Contractor's Project Director: David W. Holmes, Ph.D.

Current Annual Level of Support: \$107,615

Objectives: To conduct an experimental study of the development of communicative skills by autistic children when training involves only speech stimuli, only sign stimuli, speech and sign stimuli presented simultaneously, or speech and sign presented independently. The research will determine after six months of training which method of language training results in: Greater expressive and receptive language skills; greater use of language skills for communication; and greater retention of language skills following training. The study will also determine whether autistic children evidence cross-modality transfer of information learned in speech or sign to the other modality; whether simultaneous presentation of stimuli in two different modalities interferes with learning; and whether autistic children show similar language learning difficulties in both the speech and sign modalities.

Major Findings: Since the project was initiated in April 1979, the contractor is only in the initial stages of developing language training programs in the speech and sign modalities; procedures and criteria for subject selection; procedures for preliminary evaluation studies of the autistic subjects; behavioral coding system for evaluating communicative behavior; reliable and accurate methods for recording subjects' responses during behavior; and staff training programs for administering language training in the speech and/or sign modalities. Phase I will be complete in 12 months after initiation of the project.

Significance to NINCDS Program and Biomedical Research: Impaired speech and language development is common to all children with infantile autism although the degree of impairment varies among children. The etiology of these disorders is not known and the bases for these children's specific difficulties in learning language is not well understood. Some have proposed auditory and speech processing difficulties which could account for these impairments. Recently, there have been clinical reports of marked success with some of these children in learning language using signs or gestures and reports that once such children begin to use signs to communicate they may vocalize spontaneously and develop speech for communication more readily. This research will examine these issues experimentally and have significance for the development of improved speech and language training for autistic children.

Cooperating Units: None

Proposed Course of Contract: Once the work for Phase I has been completed and approved by the NINCDS Project Officer the experimental study will be initiated which will require two years. The final phase, involving data analysis and report writing, will run six months and be complete in October 1982.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1978 through September 30, 1979

BOSTON UNIVERSITY MEDICAL CENTER (N01-HV-5-2971)

Title: Framingham Heart Study - Hearing Assessment of Subjects

Contract Project Director: M. Stuart Strong, M.D.

Current Annual Level of Support: \$12,500

Objectives: The goal of this project is to assess the hearing sensitivity of subjects enrolled in the Framingham Heart Study and evaluate any observable relationship between sensorineural hearing loss and cardiovascular status.

Major Findings: Almost 2400 of the 3500 subjects have been evaluated. Using the criteria of 40 dB HL at 250-3,000 Hz and 50 dB HL at 4,000 and 8,000 Hz in the poorer ear, the following groups have been identified: 1) normal hearing; 2) borderline hearing; and 3) hearing-impaired. The contractor is continuing examination of the experimental cohort.

Significance to NINCDS Program and Biomedical Research: This group of subjects will provide a unique opportunity to relate hearing sensitivity and known cardiovascular findings. Vascular disease is known to be associated with some types of hearing losses but these studies have not had access to such a large and well-documented population.

Cooperating Units: National Heart Lung and Blood Institute, Biometry and Epidemiology Program of NINCDS.

Proposed Course of Contract: Upon completion of this contract and the identification of those persons with significant hearing loss, an in-depth follow-up study will be conducted to determine etiology and degree of loss by a subsequent contract. Cardiovascular data will be used in the analyses.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02185-05 CDP
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Characteristics of Dysarthric Speech Associated with Neurologic Disease		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I. C.L. Ludlow, Speech Pathologist, CDP, NINCDS C.B. Cardano, Speech Pathologist, CDP, NINCDS D.B. Calne, Clinical Director, IR, NINCDS R. Polinsky, Neurologist, LCS, NIMH		
COOPERATING UNITS (if any) IR, NINCDS; LCS, NIMH		
LAB/BRANCH Communicative Disorders Program		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .35	PROFESSIONAL: .25	OTHER: .10
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The long-range goal is to determine the characteristics of different <u>speech production disorders</u> , associated with various neurological diseases. Measurement procedures have been demonstrated to be valid for differentiating the speech production of normal <u>aging adults</u> from that of patients with <u>Parkinson's disease</u> and for measuring change in speech symptoms associated with <u>neuro-pharmacological manipulation of Shy-Drager's Syndrome, Tardive Dyskinesia and Huntington's Chorea</u> . The testing procedures include frequency and intensity calibration, a standardized testing format and normal control data for age and sex between 18 and 75 years. Acoustic analyses include <u>spectrographic</u> tracings of frequency and intensity changes over time; graphic sound intensity level recordings; and, digital signal processing to measure pitch perturbations. Completed studies have demonstrated that (a) quantitative acoustic measures are valid for assessing degree of pathology as well as for differentiating between hypokinetic		

and hyperkinetic types of dysarthria; (b) that the first evidence of pathology associated with Tardive Dyskinesia is in lingual, labial and mandibular coordination during rapid speech articulation; (c) that measures of laryngeal control differentiate Shy-Drager's Syndrome from idiopathic orthostatic hypotension in the early stages of disease.

Project Description:

Objectives:

- 1) To develop valid and reliable methods for determining and assessing the speech production problems of patients with neurologic disease.
- 2) To determine the speech production characteristics of patients with neurologic disease such as Shy-Drager's Syndrome, Parkinson's disease and Tardive Dyskinesia in contrast with those of normal aging adults.
- 3) To evaluate the effects of L-Dopa and Bromocriptine on the speech of Parkinson patients.

Methods Employed: Identical testing conditions are maintained by presenting the task instructions, calibration tone settings and models from a stimulus tape recording presented at the same intensity level. Speech recordings are made on tasks of extended phonation, loudness and pitch variation, pause and rate control, and rapid speech initiation. Measurements are made from the 34 sound spectrograms and graphic level recordings. Digital signal processing is used to measure cycle to cycle perturbation in the glottal waveform following inverse filtering.

Subjects: Patients with Parkinson's and others with Shy-Drager's Syndrome were recorded following L-Dopa and Bromocriptine in a double-blind crossover study. In other studies patients with Huntington's Chorea, Tardive Dyskinesia, Shy-Drager's Syndrome and idiopathic orthostatic hypotension were recorded when not receiving medication.

Major Findings:

Objective (1)

(a) Only acoustic measures were demonstrated to be both valid and reliable for discriminating the speech of dysarthric patients from that of normal aging controls; (b) only acoustic measures were both valid and reliable for differentiating between two kinds of dysarthria; (c) although extensive training was used to demonstrate adequate inter-judge reliability, perceptual judgements from acoustic recordings were not valid methods for differentiating pathologic from normal speech production or for discriminating between two types of dysarthria.

Therefore, all further work on speech production disorders associated with dysarthria will rely on acoustic measures. Efforts will also be made to develop movement transducers for studying neuromotor dysfunction during speech production.

Objective (2)

(a) The locus of greatest pathology in speech production in Parkinson's disease has been found to affect laryngeal control. Measures developed for assessing pathology include: rate of abduction/adduction; cycle by cycle perturbation; and modulation in fundamental frequency during sustained phonation.

(b) In early stages of Tardive Dyskinesia, pathology affecting speech production can be noted in the rapid coordination of lingual and mandibular movement.

(c) Measures of laryngeal abduction and latency during speech can differentiate between early stages of Shy-Drager's Syndrome and idiopathic orthostatic hypotension.

Objective (3)

Acoustic Analyses are still in progress for these studies.

Significance to NINCDS and Biomedical Research: The development of objective procedures for the assessment and differential diagnosis of various types of dysarthria in adults with neurological diseases, will enable researchers and clinicians to evaluate different treatments for these patients. The information being gained on which speech production processes are particularly impaired in each of the neurological diseases, will contribute to our understanding of both normal and disordered speech production as well as providing directions for treatment.

Proposed Course of Project: The following studies have been completed and are in preparation for publication: "The Effects of the On-Off Phenomenon on Speech Production in Parkinson's Disease", C. Ludlow, G. Geoffrey, R. Kartzinell and D. Calne; "A Comparison of Acoustic and Perceptual Methods for Assessing Dysarthria", C. Ludlow, C. Cardano, and B. Cullison; "Assessment of Vocal Fold Paresis in the Shy-Drager Form of Parkinsonism", D. Hanson, C. Ludlow, A. Williams, D. Calne; "Speech Production Symptoms Associated with Tardive Dyskinesia", C. Ludlow, E. Caine, and C. Cardano; and "Speech Symptoms Associated with Early Signs of Shy-Drager's Syndrome", C. Cardano, C. Ludlow, and R. Polinsky.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02247-03 CDP
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) The Characteristics and Treatment of Vocal Tics and Gilles de la Tourette's Syndrome		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I. C.L. Ludlow, Speech Pathologist, CDP, NINCDS other E.D. Caine, Staff Fellow, IR, NIMH M.H. Ebert, Chief, Section on Experimental Therapeutics, IR, NIMH C.B. Cardano, Speech Pathologist, CDP, NINCDS		
COOPERATING UNITS (if any) Section on Experimental Therapeutics, LCS, IR, NIMH		
LAB/BRANCH Communicative Disorders Program		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .35	PROFESSIONAL: .25	OTHER: .10
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A series of research studies are being conducted to determine the following: <ol style="list-style-type: none"> 1) Whether <u>Speech and Language Disorders</u> are associated with the type and severity of vocal tic phenomena in <u>Gilles de la Tourette's Syndrome</u>. 2) The characteristics of vocal tic phenomena in <u>Gilles de la Tourette's Syndrome</u>. 3) To determine the differential effects of various <u>neuropharmacological treatments</u> on the type and severity of vocal tics in patients with <u>Gilles de la Tourette's Syndrome</u>. 4) The relationship of vocal tic production to propositional language behavior. 		

Project Description:

Objectives: The following studies have recently been completed in this research area:

1. The Relationship Between Vocal Tic Symptomatology and Language Processing Skills in Patients with Gilles de la Tourette's Syndrome

Methods Employed: Forty subjects with confirmed history and current symptomatology of Gilles de la Tourette's syndrome ranging in age from five to 30 years each, were examined in the same manner as age and sex matched normal controls. None of the subjects had received medications for at least two weeks prior to examination. Standardized tests were employed to assess muscle power of the lips and tongue, oral and lingual praxis, speech articulation, and rate of repetition of oral and speech movements. Seventeen subtests of the Neurosensory Center Comprehensive Examination for Aphasia, NCCEA (Spren and Benton, 1969) were administered. A head set microphone was used to record speech during picture descriptions, oral reading and while communicating to a listener behind a screen on how to construct a block design.

Results: All subjects scored greater than two standard deviations below their age level on two or more NCCEA verbal subtests. The number and severity of subjects' verbal deficits were positively related to the number of different tic categories they exhibited. Each of those subjects exhibiting all types of tics, including jargon, were severely impaired in the construction, repetition and comprehension of sentences, word finding, reading, and writing. Conversely, the subjects with lingual and laryngeal tics only had deficits in word finding, word fluency, and sentence repetition.

These results indicate that patients with Gilles de la Tourette's syndrome demonstrate a continuum of linguistic impairment with the kinds and severities of their vocal tics related to the severity of their language performance deficits. A linguistic analysis of this disorder provides an objective and valid method for investigating patient characteristics and assessing treatment efficacy.

2. The Continuum of Vocal Tic Symptomatology Found in Gilles de la Tourette's Syndrome

All subjects were recorded during spontaneous speech production, picture description, oral reading and oral communication to an unfamiliar listener. These tasks were performed under three different test conditions; binaural presentation of white noise (WN) and binaural presentation of delayed auditory feedback (DAF).

Seven categories of vocal tics were found: Respiratory types including belches, quick inhalations and exhalations; laryngeal squeaks, barks and hums; lingual clicks; nasal snorts and sniffs; labial smacking and popping; verbal tics including partial and complete words; and phrases of coprolalia. These categories were found to represent a continuum across subjects, depending

on the kinds of tics each subject exhibited. The subjects with only three types of tics had lingual, laryngeal and respiratory tics, while those with four kinds of tics also had nasal tics. The patients with five tics produced coprolalia in addition to all preceding tic types, while only those with six and seven tic types had labial tics and jargon.

For all subjects most tics occurred on the initiation of speech and/or sentences or at constituent boundaries. Graphic level recordings and speech spectrograms confirmed that tics occurred when speech intensity level and fundamental frequency decreased. These findings indicate that tics appear during breathing for speech and speech pauses.

During both of the speech stressor conditions (WN and DAF), the rate of vocal tics increased in some subjects, while it decreased in others. However, speech dysfluencies decreased during WN in all subjects and increased during DAF in all subjects except the three who stuttered. The differential response of subjects' tic productions related to individual differences in response to haloperidol.

3. The Effects of Haloperidol, D-Amphetamine, and L-Amphetamine on Motor and Vocal Tic Production in Gilles de la Tourette's Syndrome

In a double-blind cross-over study of the acute effects of administration of haloperidol, d-amphetamine and l-amphetamine over placebo, the number and types of vocal and motor tics were recorded for each of the same six subjects at 10:00 a.m., 11:00 a.m., 12:00 noon, 1:00 p.m., 2:00 p.m., and 3:00 p.m. on alternate days for five weeks. Each recording session was uniform in format, lasted seven minutes and included five minutes of conversation and two minutes of oral reading. Counts of the relative frequency of each type of tic per minute were used in the data analysis.

Results: The relative frequencies of motor and vocal tics were not related across subjects in either the placebo or treatment (haloperidol) conditions. Also, since changes in the frequencies of motor and vocal tics across the placebo and drug conditions were unrelated, the two sets of symptoms had to be studied independently. The relative frequencies of motor and vocal tics were found to vary significantly across time of day. For example, vocal tics were fewer in the a.m. than p.m. on placebo, necessitating that all comparisons be made between samples taken at the same time of day.

Motor frequency was significantly reduced following haloperidol in the a.m., increased following d-amphetamine in the a.m. and p.m., and did not change following l-amphetamine.

Vocal tic frequency significantly decreased following both d- and l-amphetamine in the a.m. and p.m., respectively, while no significant reductions in vocal tics were noted with acute administration of haloperidol.

There were marked individual differences in responses to the three neuropharmacological manipulations. The older subjects, who had a longer history

of Tourette syndrome, had less of a reduction in motor tics with haloperidol, while those patients with the greatest numbers of vocal tics were those with the greatest reduction in motor tics with haloperidol.

Significance to Biomedical Research and to the Program of the Institute:

This research has both basic and applied significance for the understanding and treatment of this syndrome. First, the demonstration of a language performance deficit associated with vocal tic severity indicates either that the pathology involves more than basal ganglia mechanisms or that the pathology involving the basal ganglia has an effect on cortical functioning in more severe cases of this syndrome. Second, the demonstration of a continuum of vocal tic symptomatology provides a scale by which the severity of syndrome involvement can be assessed for grouping patients with similar symptoms. Previously, it has been difficult to compare patients' degrees of involvement due to vast individual differences in symptomatology. Finally, the study of the response of motor and vocal tics to acute neuropharmacological manipulations provides information on the factors which must be controlled (such as time of day, initial symptom severity, and types of tics) in future acute clinical trials of new drug treatments.

Proposed Course of Project: The three studies described above are currently being completed and will soon be submitted for publication. Further work is continuing on the effects of Gilles de la Tourette's syndrome on fluent speech production patterns and the disruption of propositional language expression and reception in school age children with Gilles de la Tourette's syndrome.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02336-02 CDP
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Early Identification of Drug-Induced Ototoxicity		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: E. Elkins, Audiologist, CDP, NINCDS Other: A. Pikus, Audiologist, CC		
COOPERATING UNITS (if any) Radiation Oncology Branch, NCI Division of Cancer Treatment, NCI Clinical Center, NIH		
LAB/BRANCH Communicative Disorders Program		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .30	PROFESSIONAL: .30	OTHER: .00
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Certain <u>pharmaceutical agents</u> used in the treatment of cancer are known to have toxic effects upon the hearing of patients. <u>Cochlear damage</u> is manifested by a high-frequency <u>hearing loss</u> and general difficulty in understanding normal speech conversation. Periodic assessment of pure tone thresholds and supra-threshold speech perception are being conducted to evaluate and relate degree and progression of <u>ototoxicity</u> to drug dosage and frequency of administration.		

Project Description:

Objectives: To develop techniques for the assessment of ototoxicity related to the administration of certain chemotherapeutic agents employed in cancer treatment. The following areas are being addressed: a) type of hearing loss, b) onset and degree of loss relative to dosage and preexisting hearing condition, c) documentation of onset of tinnitus and/or vertigo, d) predisposition to ototoxic effects, e) unilateral/bilateral symmetrical loss, f) suprathreshold speech perception, g) prediction of probable ototoxicity, and h) possible reversibility of ototoxic effects.

Methods Employed: In addition to routine procedures, monosyllabic speech stimuli are presented at various signal-to noise ratios (S/N) and at different levels above puretone or speech reception threshold levels.

Major Findings: Phase I results showed that a +10 dB S/N using consonant-nucleus consonant monosyllabic stimuli did not significantly degrade subjects' speech perception when compared to normal performance on the same task. Phase II is incorporating a more difficult S/N. Upon completion of an adequate number of patient evaluations, multiple regressions will be performed on the data in an attempt to develop a predictive profile of patients particularly susceptible to ototoxic effects of the drugs under study.

Significance to NINCDS and Biomedical Research: The development of repeatable and valid methods of assessing hearing impairment following the administration of known drug dosages would provide the clinician with documentation for the managing physicians who in turn may reassess their drug protocols. A reliable method of predicting ototoxicity is definitely needed if prevention of impairment is to be realized.

Proposed Course of Project: Further investigation will be given to the problems and procedures identified above with a patient population available through cooperation with the National Cancer Institute.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02337-02 CDP
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) The Effects of Dextroamphetamine on the Communicative and Language Skills of Hyperactive Subjects		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="margin-left: 40px;"> P. I. C.L. Ludlow, Speech Pathologist, CDP, NINCDS J.L. Rapoport, Psychiatrist, IR, NIMH G.L. Brown, Psychiatrist, IR, NIMH C.B. Cardano, Speech Pathologist, CDP, NINCDS </div>		
COOPERATING UNITS (if any) Section on Experimental Therapeutics, LCS, IR, NIMH		
LAB/BRANCH Communicative Disorders Program		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .50	PROFESSIONAL: .25	OTHER: .25
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <p>The purpose of the research is to determine whether dextroamphetamine--a stimulant drug therapy--has a beneficial effect on the <u>language</u> performance, speech reception and <u>communicative</u> skills of different groups of <u>normal</u> and learning disabled boys: <u>hyperactive</u> boys with <u>impaired language development</u>, hyperactive boys with normal language and impaired communicative skills, and normal boys.</p> <p>Dextroamphetamine was found to have a beneficial effect on the language and communicative skills of all three groups studied, although the effects differed in each group. The groups most benefited by drug administration were the normal subjects whose task directed communicative speech increased in fluency and complexity. Both hyperactive groups were benefited. Those impaired in language development increased most in their speech fluency and language task performance while those only impaired in communication were only aided by a decrease in their non-task directed speech. Communicative</p>		

speech fluency was most increased in the normal subjects and language impaired subjects and least in the hyperactive subjects.

Objectives:

The following questions have been or are currently being examined in various studies which comprise this research.

- 1) Whether dextroamphetamine has a beneficial effect on language expression, reception and communicative ability of the following four groups: normal boys and normal adults, hyperactive boys with normal language development, language impaired hyperactive boys.
- 2) Whether acute administration of dextroamphetamine improves the auditory processing deficits of language impaired hyperactive boys.
- 3) Whether the acute administration of stimulant drugs improves the speech discrimination skills of language impaired hyperactive boys.

Procedures: The following procedures are administered to all four groups.

- 1) Three experimental language sampling tasks--picture description, story telling and a communication task requiring instruction of a "blind" listener on block design construction.
- 2) Experimental acoustic perception tasks assessing detection of tones in noise; a fifteen minute vigilance task; a gap detection task with various gap size intervals; and, a temporal order task with various inter-stimulus intervals.
- 3) Speech discrimination tests including the Goldman, Fristoe, Woodcock "Test of Selective Attention."

Analysis procedures include:

- 1) Transcription of the speech samples and computation of the relative frequency of the following language behaviors relative to one minute of child's speech was computed: task directed speech, descriptive speech, complex sentences, grammatical sentences, child initiated speech commands, questions, refusals, echolalia, stereotypic speech and perseverative speech. Language complexity measures included mean length of utterance, grammatical complexity, and speech rate. Measures of communicative speech included the proportion of task directed commands, descriptive task directed statements and story telling length.
- 2) Scoring of one block design construction made by trained listeners "blind" as to speaker identity, the target design and testing condition when responding

to subjects' directions contained on tape recordings.

3) Psychometric functions were computed using the available data points to identify threshold (s) values for the gap detection and temporal order tasks.

Results:

1) The language impaired hyperactive subjects (LIH) were compared with the normal (N) and the non-language impaired hyperactive subjects (NH). The effects of dextroamphetamine on the language performance of the three groups differed. The normal subjects showed marked increases in their task directed speech while their disruptive speech was further reduced. In contrast, the hyperactive subjects in group NH decreased in their amount on non-task directed speech but did not change in their amount of speech with stimulant treatment.

The response of the language impaired hyperactive subjects to stimulant drug treatment was very similar to that on the normal subjects and not the NH group. The LIH group significantly increased in their total amount of speech and their task directed speech, while their disruptive speech decreased with stimulant administration. Significant increases in linguistic complexity occurred in all three groups with stimulant drug administration.

2) When the accuracy of the subjects' directions was assessed by listeners' scores on the block design task, the hyperactive children's scores were significantly lower than the normal subjects' on placebo ($p < .05$). Thus, communicative performance was affected independently from verbal ability since the hyperactive subjects were equal to the normal subjects on tests of language development.

Changes in communicative performance with the administration of dextroamphetamine differed in the two groups. Only the hyperactive subjects increased in communicative accuracy with dextroamphetamine. At the same time, the hyperactive subjects also improved in their organization and sequencing of directions and grammaticality. A linguistic analysis of the hyperactive subjects' speech demonstrated that with dextroamphetamine, the frequency of sentence embedding significantly increased ($p = .04$).

The normal subjects did not increase in their communicative accuracy, but were judged to increase in the amount of information contained in their directions. In addition, the amount of speech they produced increased with dextroamphetamine ($p = .04$) although speech rate did not change in either group.

Research is still ongoing examining effects of stimulant drugs on auditory processing and speech discrimination skills.

Significance to NINCDS Program and Biomedical Research: The importance of studying language performance behaviors when studying stimulant drug treatment was demonstrated. Acute administration of stimulant drugs was found to enhance the language performance of language impaired hyperactive children by improving their language grammaticality, speech fluency and amount of task directed speech. The results indicate that stimulant drug treatment might be a useful adjunct to the treatment of impaired language development in hyperactive children.

In addition, methods were developed for objectively assessing communicative ability in normal and language impaired children and demonstrated that communicative performance can be impaired independent from language ability in hyperactive children and that such children are less accurate than normal in their communicative speech due to poor organization, sequencing, clarity, incomplete sentences and fewer descriptive instructions. These findings have immediate treatment implications.

Proposed Course of Project: At present the following manuscripts are being prepared for publication: "The Effects of Stimulant Drug Treatment on Language Performance in Language Impaired and Non-Language Impaired Hyperactive Boys", C. Ludlow, C. Cardano, G. Brown, and J. Rapoport; and "Communicative Abilities of Hyperactive and Normal Children and Drug Effects", C. Ludlow, B. Richards-Munn, and B. Cullison.

Work is continuing on the studies of auditory processing deficits and their relationship to language impairments and the effects of stimulant drug therapy on these functions.

Publications:

Ludlow, C. L., Rapoport, J. L., Cardano, C. B., and Mikkelsen, E. G. Differential effects of dextroamphetamine on language performance in hyperactive and normal boys. In R. M. Knights and D. J. Bakker, (Eds.), Treatment of Hyperactive and Learning Disordered Children: Recent Research. Baltimore, University Park Press, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02395-01 CDP
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Analysis of Fluctuating Hearing Loss Associated with Cogan's Syndrome		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: A. Pikus, Audiologist, CC Other: B.F. Haynes, LCI, NIAID E. Elkins, Audiologist, CDP, NINCDS		
COOPERATING UNITS (if any) Clinical Center, NIH Laboratory of Clinical Investigation, NIAID		
LAB/BRANCH Communicative Disorders Program, NINCDS		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER: .00
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) To <u>assess</u> the course of the <u>auditory deficit</u> associated with <u>Cogan's Syndrome</u> . One patient has been audiologically evaluated weekly or biweekly relative to steroid dosage and institution of diuretic therapy. <u>Speech discrimination</u> , tolerance (UCL), <u>tympanometry</u> and <u>acoustic reflex</u> responses have been followed closely.		

Project Description:

Objectives: To develop accurate audiologic indices of the pattern of hearing deficit in Cogan's Syndrome and to document relationship of hearing deficit to chemotherapy.

Methods Employed: Standard audiologic test battery is utilized weekly or biweekly including middle ear analysis. Special auditory tests are repeated intermittently to verify the cochlear nature of the auditory effects of this disease process.

Major Findings: To date, hearing fluctuations appear unrelated to prednisone dosage. However, following a glycerin test some small puretone improvement and marked improvement in suprathreshold discrimination for speech ability was demonstrated. Since the dosage of steroids has been reduced and diuretic therapy instituted, there have been fewer and smaller negative fluctuations in pure threshold responses and suprathreshold discrimination ability seems to have remained good (to excellent) even with accompanying downward puretone shifts. Tympanometric abnormalities and changes have been documented over a six-month period (to date) as have acoustic reflex measurements which have shown a return after a lengthy period of no response or elevated response.

Significance to NINCDS and Biomedical Research: The development of an audiological profile of subjects with Cogan's Syndrome should provide clinicians with information for successful management of these patients.

Proposed Course of Project: Continued investigation of additional Cogan's Syndrome patients will be carried out through cooperation with the National Institute of Allergy and Infectious Diseases and the National Eye Institute.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02396-01 CDP
PERIOD COVERED January 1, 1979 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Collagen Metabolism in Osteogenesis Imperfecta		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: J.R. Shapiro, CC Other: A. Pikus, Audiologist, CDP, NINCDS E. Elkins, Audiologist, CDP, NINCDS E. Gross, Chief, Section on Molecular Structure, ERRB, NICHD J.W. Hansen, NICHD S. Levin, Dept. of Otolaryngology, Johns Hopkins University G. Martin, NIDR K. Rosenbaum, Dept. of Genetics, Children's Hospital, Washington, DC D. Rowe, Dept. of Pediatrics, University of Connecticut		
COOPERATING UNITS (if any) Laboratory of Developmental Biology and Anomalies, NIDR; Clinical Center, NIH; Section on Molecular Structure, ERRB, NICHD; Neonatal and Pediatric Medicine Branch, NICHD; Johns Hopkins University; University of Connecticut; Children's Hospital, Washington, D. C.		
LAB/BRANCH Communicative Disorders Program		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .20	PROFESSIONAL: .20	OTHER: .00
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Methods are being developed to delineate the types of hearing losses associated with <u>Osteogenesis Imperfecta</u> (OI). Measurement of <u>middle ear function</u> by tympanometry and acoustic reflexes are being employed to classify patient responses and identify <u>carrier status</u> .		

Project Description:

Objectives: This study evaluates all OI patients for audiologic abnormalities using the standard threshold and suprathreshold techniques with special emphasis on middle ear analysis, in an effort to classify the different kinds and severity of hearing loss and perhaps identify carrier status in certain types as well as middle ear factors related to prognosis for future audiologic deficit. Complete families of patients are now being evaluated as well.

Methods Employed: Routine audiologic battery: consisting of threshold pure-tone and speech measurements; suprathreshold discrimination for speech testing; tolerance levels for speech under headphones (UCL); tympanometry and the measurement of contralateral acoustic reflexes. Special auditory tests are administered as indicated.

Major Findings: Substantial anomalies in middle ear analysis have been found across all types of OI. Tympanometry and acoustic reflexes are abnormal for a large proportion of patients seen to date. Abnormal tympanometry and acoustic reflexes have been found in all OI patients above age ten. In one family to date, "OI tympanograms" were found in an unaffected mother.

Significance to NINCDS and Biomedical Research: Identification of carrier status in OI by means of an easily administered audiologic evaluation would have great value in the management of families in which OI is prominent.

Proposed Course of Project: This project is ongoing and will continue to assess the parameters mentioned above.



ANNUAL REPORT

October 1, 1978 through September 30, 1979

Fundamental Neurosciences Program

National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
October 1, 1978 - September 30, 1979
Fundamental Neurosciences Program
National Institute of Neurological and
Communicative Disorders and Stroke

Basic research in the neurosciences is supported by all four Extramural Programs. However, the Fundamental Neurosciences Program (FNP) is especially concerned with those projects that are not obviously disease-related and serve to broaden and expand the store of scholarly information in the classic disciplines of neuroanatomy, neurophysiology, neurochemistry and neuropharmacology. This is the base upon which clinical research is ultimately dependent, not only for information, but for the development of techniques and methodologies which make applied research feasible. The FNP is divided into three subprograms: General Fundamental Neurosciences, Neural Prosthesis, and Biomedical Engineering.

Characteristically, FNP is assigned approximately one-fourth of the grant applications received by NINCDS and, of these, about 90% are recommended for approval by initial review groups. During FY 1979, over 50% of those approved were funded. The portfolio currently contains about 422 regular grants and 10 program projects supported at a level of approximately 28 million dollars.

The Neural Prosthesis Program, directed by Dr. F.T. Hambrecht, is an important aspect of FNP activity. It is primarily oriented toward the study and solution of problems at the interface between electrodes and nervous tissue, issues which must be satisfactorily resolved before the chronic implantation of devices to compensate for lost sensory or motor capacities. These involve the effects of various parameters of electrical stimulation such as duration, direction and intensity of current flow, electrode design, electrode toxicity, and changes in electrode and tissue properties over time. This program, one of the few of its kind in the world, is primarily supported through research contracts at a level of about 2 million dollars a year.

GENERAL FUNDAMENTAL NEUROSCIENCES

This is the largest of the subprograms. It includes almost all of the research grants assigned to the Fundamental Neurosciences Program as well as several contracts.

Regular Research Grants and Program Project Grants

As of July 1, 1979, there were 422 regular research grants and ten program project grants in the program: (see Table)

ACTIVE GRANTS DURING JULY 1979

REGULAR RESEARCH GRANTS

PROGRAM PROJECT GRANTS

	No.	% of Total	\$	% of Total	No.	% of Total	\$	% of Total
Neuroanatomical Sciences	65	15.5%	3,531,114	14%	2	20%	754,969	25%
Neurophysiological and Neurophysical Sciences	154	36.5%	9,246,168	36%	4	40%	869,275	28%
Biochemical Sciences	170	40%	11,053,994	43%	3	30%	1,178,559	38.5%
Biological Sciences	13	3%	653,472	2.5%				
Psycho-Biological Relationships	16	4%	835,471	3.5%				
Neural Prostheses and Biomedical Engineering*	4	1%	230,604	1%	1	10%	259,749	8.5%
TOTALS	422	100%	25,550,823	100%	10	100%	3,062,552	100%

*These grants are part of the subprograms in Neural Prosthesis and Biomedical Engineering. They are listed for completeness, but are described below under the appropriate subprogram.

It should be noted that the program only includes those basic neuroscience grants which are not directly disease-related and thus represents only a fraction of NINCDS-supported work on neural structure and function.

Progress reports from FNP grantees reveal much new scientific knowledge. Three examples are given here:

The structure of the nerve membrane is most often inferred from its electrical properties and by chemically or pharmacologically induced changes during voltage clamping. Alternatively, the properties of various model systems (lipid and protein bilayers) are measured in the presence of physiologically important ions. A potentially important unusual preparation in this regard is the electrically inexcitable crustacean muscle fiber which can be induced to fire repetitively after treatment with compounds that react with sulfhydryl groups. Calcium channels are involved in inward current, but the molecular reconfiguration of the membrane is not known. However, by suitable use and modification of sulfhydryl reagents, additional insight into the structure of the excitable membrane should be forthcoming.

The study of axon transport is illustrative of the difficulties and complexity of research in a maturing classical area. A problem of current interest concerns the metabolic relationships between the axon, myelin sheath and Schwann cell. Cholinephosphoglycerides transported down the axon, apparently can be directly transferred to the inner myelin leaflets, while in the outer leaflets the same compound originates from Schwann cell synthesis. In contrast, there is no evidence that the myelin proteins or glycoproteins are derived intact from axonal flow. Using two-dimensional gel electrophoresis, at least 60 independent protein species can be designated as "rapidly" transported, although the functional identity of only a few has been established. On the other hand, axotomy may induce a reorganization of the protein synthesizing machinery in neurons, leading to an increase in the synthesis of structural proteins for axonal regeneration and a decrease in the synthesis of functional proteins required for synaptic transmission-tyrosine hydroxylase, choline acetyltransferase, and acetylcholinesterase.

Few laboratories are currently concerned with the neurophysiology of the peripheral autonomic nervous system, despite the widespread interest in the processes of acquiring voluntary control of blood pressure and vasomotor activity for the amelioration of hypertension and migraine. Yet, even control of the heart rate is imperfectly understood. Recent studies have shown that the vagus and cardioaccelerator nerves fire reciprocally in the classical mode only under certain circumstances and simultaneous activation of both nerves may normally occur, the resultant heart rate a product of the vector sum of divergent influences. The principle may be common in the autonomic nervous system and is reminiscent of the situation at CNS synapses, where both inhibitory and excitatory inputs infringe upon the post-synaptic membrane. Illustrative of recent research in this area are the effects of baro- and chemoreceptor input on the neurosecretory neurons of the supraoptic and paraventricular nucleus of the hypothalamus. Stimulation of baroreceptors inhibits neuronal activity while activation of the chemoreceptors strongly excites these cells. Afferent impulses from the sinus and aortic nerves may reach the supraoptic nucleus via the tractus solitarius of the medulla and the shortest latency of responses in this instance is about 10 msec. However, most impulses reach the nucleus through

long polysynaptic pathways with a latency of 50-70 msec. suggesting that temporal or spatial summation of inputs is required to exert inhibitory or excitatory effects on these neurons.

Local Neuronal Interactions

As a result of a Program Announcement issued last year, a large number of detailed inquiries were received. Interest still continues at a high level. At Study Section meetings for the May Council, 33 grant applications that were submitted in response to the announcement were received. Twelve of these have been funded since the Council meeting; the total funds committed are \$610,000.

Additional applications and inquiries continue at a rate exceeding original expectations. Considerable interest is being shown also by foreign investigators, and applications have been received or are being prepared from England, Canada, Switzerland and Hungary.

Neuroanatomical Asymmetry in the Human Temporal Lobes

A project being conducted under research contract with McMaster University is concerned with the investigation of relationships between temporal lobe asymmetry and psychological characteristics. Currently, forty-six cancer patients have elected to participate in this unique research effort.

Neuroimmunomodulation

An area of research which has received scant attention in the U.S. is that of central nervous system influences on general immune and allergic responses. At the Twenty-eighth World Congress of Physiology in Budapest, Hungary in July 1980, the first formal international symposium on Neuroimmunomodulation will be convened. This is the logical sequence of six years of preparation at the International Union of Physiological Sciences. At a satellite meeting of the Twenty-sixth World Congress, a member of the FNP reviewed the field of Central Nervous System Influences on Immune Responses for the Symposium "Recent Developments in Physiology", (Teheran, 1974). At the Twenty-seventh World Congress (Paris, 1977) he organized a meeting on this subject, as a result of which an informal world "club" of investigators in this field was founded. In preparation for the 1980 Congress, and in an effort at both survey and education, he spent two and a half weeks in Hungary, Rumania, Switzerland and Greece, visiting laboratories, lecturing and planning cooperative research in neuroimmunomodulation. Under the stimulus of the Fundamental Neurosciences Program this new, intriguing and underdeveloped science is rapidly gaining recognition. At the most recent meeting of the FNP Advisory Committee a proposed conference on neuroimmunomodulation was unanimously endorsed and given highest Program priority.

Scientific Information Exchange

FNP has supported two information exchange contracts, the Brain Information Service (BIS) at UCLA and the Neurosciences Research Program (NRP) at M.I.T.

BIS has made available current alerting bulletins, recurrent bibliographies, reference bibliographies and conference reports covering areas of interest to basic neuroscientists. Recent studies have indicated that the data base of the National Library of Medicine and the retrieval systems servicing it have now developed to the stage where they can provide neuroscientists with a satisfactory, effective means of searching through the neuroscience literature and of obtaining routine monthly surveys tailored to a scientist's work. Thus, the BIS contract will be terminated in early 1980.

The NRP continues to provide a unique service by bringing together periodically a large number of the best neuroscientists to re-examine various areas of neuroscience. Proceedings of these conferences are published rapidly in the Neurosciences Research Program Bulletin. For example, a Cerebral Cortex Colloquium was held at Woods Hole, Massachusetts, April 29 to May 4, 1979, which was attended by more than 30 invited neuroscientists and many of the NRP staff. Unlike most such colloquiums, the topics went from the molar to the molecular. Sessions dealt with higher brain function, connections of the neocortex, its microorganization, its development, plasticity and evolution, and chemical signaling. The final session dealt with theoretical constructs and models. A volume composed of the papers will be published within a year. Support for NRP was switched from the contract mechanism to the grant mechanism during the fiscal year.

NEURAL PROSTHESIS

The attached narratives give brief descriptions of recent findings resulting from contract research. It is encouraging to note that safe ranges of stimulation for various types of stimulation have been determined, new biomaterials have been introduced, and new types of electrodes have been developed. These fundamental studies are providing the new knowledge and new techniques that will serve as the foundation for future neural prostheses.

Many basic scientists have become interested in this work, and its acceptance has increased. This is reflected in an increased number of approved and funded grant applications in the field. For example, during the past year the Neural Prosthesis Program has added grants on microprocessor controlled stimulation of muscles in paralyzed individuals and on prostheses for evacuation of the neurogenic bladder. The Neural Prosthesis Program has also recently published a Program Announcement requesting grant applications involving studies of modifications of neural activity by applied electrical fields. The results of such studies will be used to improve the design of future neural stimulating electrodes. (See appendix)

BIOMEDICAL ENGINEERING

The Biomedical Engineering Program consists of one contract for the development of transdermal stimulators (for auditory prostheses, cerebellar stimulation in studies of movement disorders, and for bladder evacuation), two regular research grants, and one program project grant. The latter is involved in the design and development of state-of-the-art instrumentation for both basic and clinical neuroscience research.

The program emphasis will continue to be concentrated on responding to the needs of basic and clinical researchers by supporting the design and development of devices and instrumentation which are not commercially available or which could not be produced commercially without a significant amount of research and development.

APPENDIX

PROGRAM ANNOUNCEMENT

The FNP Advisory Committee gave highest Program priority to a new contract or grant for studying the mechanisms of activation of cortical neurons by applied electrical fields produced by arrays of implanted electrodes. In response to this mandate FNP issued the following Program Announcement in the May 11, 1979 issue of the NIH Guide for Grants and Contracts.

Modification of Activity of Defined Cerebral Neuronal Populations By Applied Electrical Fields

The Fundamental Neurosciences Program of the National Institute of Neurological and Communicative Disorders and Stroke is seeking research grant applications involving modification of activity of defined cerebral neuronal populations by applied electrical fields [legislative authority is found in Section 301 of the Public Health Service Act (P.L. 78-410, 42 USC 241); Catalog of Federal Domestic Assistance Number is 13.854]. It is expected that the research resulting will provide knowledge useful in the development of neural prostheses.

BACKGROUND

Most neural prostheses presently being investigated subject neural tissue to electric fields generated by remote electrodes. It is assumed that these fields depolarize neural membranes causing the generation and propagation of neural activity. In the case of prostheses that utilize stimulation of peripheral nerves, such as in the electrophrenic respirator, the effectiveness and extent of stimulation can be readily monitored by observing the contractions of the diaphragm. However, little is known about the effects of stimulating currents from cerebral electrodes on central nervous system (CNS) neurons. An increased understanding of the interaction of external fields with individual CNS neurons would be of value in the design of electrode arrays, in understanding the basis of the motor and perceptual effects of stimulation, and in delineating stimulation parameters that optimize the desired effects while minimizing the deleterious effects.

It is anticipated that initial studies would include intracerebral electric field plots of the electrodes to be tested over the range of anticipated stimulus parameters. Using extracellular and intracellular recording techniques the spatial extent of direct versus synaptic excitation and/or inhibition would be determined. The temporal unit firing characteristics including the latency of activation and possible afterdischarges are important in estimating information transfer rates.

The long-range feasibility of certain types of sophisticated neural prostheses will most likely depend on the successful development of safe and effective intracerebral stimulating electrodes. Several investigators have used microstimulation techniques and have made estimates on the extent

of neuronal activation. These studies need to be repeated with intracerebral electrodes suitable for prostheses and results compared with those obtained with cortical surface stimulating electrodes. It is known that the charge required to stimulate cortical neurons decreases as the electrode size is reduced and the electrode is moved closer to the neurons. However, the current density and charge density required for stimulation increase with the smaller size. This can cause undesirable electrode oxidation-reduction reactions. The exact relationships involved in this trade-off need to be studied.

The techniques developed for this work would also be applicable to further understanding of the effects of electrical stimulation on cerebellar neurons and spinal neurons which are two other central nervous system areas currently being used as sites for neural prostheses. Extension to these areas will depend on results from the cerebrum.

SCOPE OF RESEARCH

The proposed studies should be carried out in mammals utilizing monopolar, bipolar, and concentric electrode configurations. A number of different sizes of electrodes should be employed with different geometries appropriate for activating specific neuronal populations. Stimulus parametric sets must be carefully chosen to be physiologically effective but to produce little or minimal damage when applied over a long period of time. Correlation of experimental findings with theoretical models may be desirable.

The effectiveness of various electrode geometries and stimulus parametric sets needs to be evaluated in terms of:

1. the location and extent of affected neuronal populations
2. the size and type of cells activated
3. the part of the cells where initial activation occurs
4. whether direct or synaptic excitation or inhibition occurs or whether mean firing rates are increased or decreased on a statistical basis
5. the spatial and temporal characteristics of any after-discharges induced by the stimulation, and
6. the input-output relationships of the activated cell populations.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 - September 30, 1979

Contractor: University of California at Los Angeles, Brain Information Service (UCLA-BIS) (NO1 NS 9-2304)

Title: Operation of Specialized Information Center in Brain and Other Neurosciences

Contractor's Project Director: Michael H. Chase, Ph.D.

Current Annual Level of Support: \$330,000

Objectives: The contractor operates a specialized information center, which serves as a national focal point for the identification, collection, storage, retrieval, analysis, repackaging, and dissemination of information on non-clinical neurosciences. The major thrusts of this information center are information analysis products and services using the identified and stored information. The contractor makes available comprehensive information services, including: current alerting bulletins, recurrent bibliographies, reference bibliographies, and conference reports.

Major Accomplishments: During the current contract period, the Brain Information Service is carrying out the following activities:

Current Alerting Bulletins

Neurochemical Transmitters and Modulators
Neuroendocrine Control Mechanism: Hypothalamic-Pituitary-Gonadal System
Sleep Bulletin including Sleep Reviews
Memo of Current Books in the Brain Sciences (Incl. Author Index)
Developmental Neurobiology

Recurrent Bibliographies

Neuroimmunology
Cerebral Evoked Potentials
Endorphins

Bibliographic Cumulations

Bibliography on the Hypothalamic-Pituitary-Gonadal System
Biogenic Amines in the Central Nervous System, A Bibliography
A Bibliography of Electrical Recordings in the CNS and Related Literature
Sleep Research

Conference Report

Annual Meeting of the Society for Neuroscience
Annual Winter Conference on Brain Research

Significance to Biomedical Research and the Program of the Institute: The Brain Information Service has served the biomedical community by the maintenance of a very extensive data base devoted to the fundamental neuroscience literature. In addition, a number of synthetic and analytic information products are produced by the staff for distribution to the neuroscience community.

Proposed Course of the Contract: The program has been under the continuing surveillance of the NINCDS Project Officers and the BIS National Scientific Advisory Committee. Each product receives detailed review.

It is proposed to discontinue this contract activity on January 14, 1980. Recent studies have indicated that the data base of the National Library of Medicine and the retrieval systems servicing it have now developed to the stage where they can provide neuroscientists a satisfactory, effective means of searching through the existing neuroscience literature and of obtaining routine monthly surveys tailored to a scientist's work. Steps have been initiated to advise the neuroscience community of the availability of these services.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: HUNTINGTON INSTITUTE OF APPLIED MEDICAL RESEARCH (N01-NS-0-2275)

Title: Studies to Determine the Feasibility of a Sensory Prosthesis

Contractor's Project Director: William Agnew, Ph.D.

Current Annual Level of Support: \$200,315

Objectives: The histopathological effects of long-term electrical stimulation of the nervous system in animals are being studied with various electrode designs, stimulus wave forms, and stimulus parameters. These studies include the effects on neurons, glia, blood vessels, and meninges. These tissues are examined with both light and the electron microscope.

Major Findings: 1. Neural damage in the cerebral cortex of cats increases with charge density over a range of 40 to 400 microcoulombs/cm² per phase despite the maintenance of constant total stimulus charge. 2. Platinum dissolution was quantitated in cat brain tissue surrounding stimulation electrodes. Values ranging from 1.6 to 11.4 micrograms/gram (wet weight of tissue) were found in the first millimeter beneath active electrodes with lesser, but detectable amounts within the second millimeter. 3. A porous type matrix constructed of Dacron mesh has proven to be the superior support material for brain surface electrodes with respect to minimal compression of the cortical surface.

Significance to Biomedical Research and to the Program of the Institute: These studies are important for determining the safety and efficacy of various forms of neural stimulation utilized in neural prostheses for the neurologically handicapped.

Proposed Course of Contract: This contract will terminate in December 1979.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: MASSACHUSETTS GENERAL HOSPITAL (N01-NS-0-2276)

Title: Studies to Determine the Feasibility of a Sensory Prosthesis

Contractor's Project Director: Daniel Pollen, M.D.

Current Annual Level of Support: \$0

Objectives: The mechanisms of neuronal activation resulting from electrical stimulation of the central nervous system are being studied. Methods of reducing the latency of activation of neurons and methods of preventing afterdischarges are being developed.

Major Findings: 1. The distribution of cortical cell types in the striate cortex of the cat which are activated by single shock electrical stimulation of the cortical surface and by stimulation of the optic chiasm has been determined as a function of stimulus level.

Significance to Biomedical Research and to the Program of the Institute: An understanding of the mechanisms of activation of visual cortex neurons by electrical stimulation is important for the development of sensory prostheses.

Proposed Course of Contract: This contract was terminated in June 1979.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF ROCHESTER (N01-NS-0-2279)

Title: Development of a Sensory Prosthesis

Contractor's Project Director: Robert Doty, M.D.

Current Annual Level of Support: \$93,800

Objectives: The stability of the threshold of excitation of nerve cells of the visual cortex during long-term electrical stimulation is being studied in monkeys. The mechanisms causing increases in threshold for detection of stimulation and means of preventing the increases are being evaluated. The effects of chronic blindness and various stimulus modulation schemes on information transfer rates are also being studied.

Major Findings: 1. A statistically significant but small change in access resistance of electrodes in striate cortex was demonstrated consequent to prolonged dark adaptation versus bright illumination. 2. For electrodes with small surface areas (less than $2.5 \times 10^{-4} \text{ cm}^2$), there is a significant inverse correlation between access resistance and threshold for detection of stimulation in striate cortex. 3. Both Dutch Belted and New Zealand white rabbits have been found to be prone to both overt and latent epileptic seizures at levels of cortical stimulation that are safe in monkey and in man.

Significance to Biomedical Research and to the Program of the Institute: This work will be useful for developing safe and efficient methods of stimulating the central nervous system for use in neural prostheses for the neurologically handicapped.

Proposed Course of Contract: Due to the death of the Project Director, Dr. John Bartlett, this contract will be terminated in December 1979.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF FLORIDA (N01-NS-1-2286)

Title: Electrode Material Study

Contractor's Project Director: William W. Dawson, Ph.D.

Current Annual Level of Support: \$0

Objectives: The development and evaluation of electrode conductors and insulators for neural prosthetic implants.

Major Findings: 1. Administration of prednisone (1mg) before each stimulation session does not prevent damage to cortical tissue from electrical stimulation compared with identically stimulated control animals. 2. Unstimulated rhodium electrodes do not produce histopathological evidence of cortical damage. This contradicts previous findings on this contract and raises the question of the purity of the original rhodium used. 3. Utilizing the d-oxyglucose method of quantification for local glucose utilization, a marked elevation in cortical metabolism directly beneath stimulating electrodes has been demonstrated. This elevation is asymmetrical extending much further in the medial and lateral directions compared with the extension in the anterior and posterior directions.

Significance to Biomedical Research and to the Program of the Institute: The evaluation and development of electrode materials is necessary for all devices that utilize electrical stimulation of excitable tissues. The addition of rhodium as a safe and effective material for electrode construction adds an additional biomaterial for use in prosthetic design.

Proposed Course of Contract: This contract was terminated in October 1978.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: CASE WESTERN RESERVE UNIVERSITY (N01-NS-2-2314)

Title: Study of Intramuscular Electrical Stimulation of Muscle

Contractor's Project Director: Thomas Mortimer, Ph.D.

Current Annual Level of Support: \$237,880

Objectives: Both animal studies and muscle implant studies in humans are directed toward the development of proportional control of the upper extremities in paralyzed individuals. Methods of reversing disuse atrophy, preventing muscle fatigue and providing smooth, coordinated muscle contractions are being investigated. In a separate project, stimulation of the paravertebral muscles through percutaneous electrodes in patients with scoliosis is being evaluated.

Major Findings: 1. The contraction time of muscles which are stimulated while held at a fixed length is longer than when the muscle length is allowed to change. Also, certain muscle fiber types appear to atrophy when stimulated at fixed lengths (full extension). 2. Multistrand, stainless steel lead wires have significantly longer lifetimes than singlestrand, stainless steel leads. 3. Both proportional and integral control in closed-loop force feedback systems have been extended to human subjects. Steady state linearity, stability and adequate response time have been demonstrated. A ratio of approximately 10 to 1 of integral to proportional gain appears to be optimal. 4. Five patients with scoliosis have now been implanted with paravertebral electrodes. In two of the patients, the spinal curvature has progressed slightly requiring the addition of a Milwaukee brace. Two of the patients have experienced no change in curvature since initiation of stimulation.

Significance to Biomedical Research and to the Program of the Institute: The techniques being investigated are intended to restore lost function in paralyzed individuals and lead to an effective treatment for scoliosis.

Proposed Course of Contract: This is a long-range project for solving basic neuroscience and clinical engineering problems associated with the development of totally self-contained stimulation systems that allow quadriplegic patients to regain control of their paralyzed muscles. Long-term objective measurements of curvature in patients with scoliosis treated by electrical stimulation of the paravertebral muscles will be pursued. During the next few years, the addition of feedback transducers and their integration into closed-loop feedback control systems for quadriplegic patients will be emphasized.

Cooperating Units: Laboratory of Neural Control, Intramural Research Program, NINCDS.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-3-2307)

Title: Studies of Urinary Bladder Evacuation by Electrical Stimulation

Contractor's Project Director: Emil Tanagho, M.D.

Current Annual Level of Support: \$97,509

Objectives: Studies are being conducted in animals with upper motor neuron lesions to determine the feasibility of urinary bladder evacuation by electrical stimulation of the sacral spinal roots. Studies are also being carried out on methods of preventing urinary incontinence.

Major Findings: Before implantation in humans, chronic animal testing of prototype systems must be completed. At the present time, five spinal animals have been implanted and are undergoing chronic testing.

Significance to Biomedical Research and to the Program of the Institute: The ability of a person with a neurogenic bladder to empty his bladder voluntarily is the long-range goal of this work and would reduce urinary tract infections that are a major cause of death in paraplegics and quadriplegics. The problem of urinary incontinence is of both social and medical significance, especially in the geriatric population.

Proposed Course of Contract: Following five months of implantation and bladder evacuation in five spinal dogs, the bladder evacuation system will be implanted in humans with neurogenic bladders. Following implantation, an extensive evaluation of the bladder pressure developed, flow rates, etc. will be conducted.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: EIC CORPORATION (N01-NS-3-2313)

Title: Safe Procedures for Electrical Stimulation of the Nervous System

Contractor's Project Director: Barry Brummer, Ph.D.

Current Annual Level of Support: \$87,750

Objectives: The electrochemical properties of both metal and capacitor electrodes are being studied. Potential toxic reaction products and their relationships to electrode design and stimulus parameters are being evaluated.

Major Findings: 1. An oxygen-measuring electrode based on the rate of platinum electrode potential decay has been developed to measure oxygen concentration in vitro. 2. The tendency for anodic-first pulses to cause more dissolution of metal electrode surfaces than cathodic-first pulses was confirmed. 3. At least 2% horse serum albumin in solution is required to arrest platinum dissolution during pulsing. 4. Platinum content in brain tissue beneath stimulation electrodes has been measured.

Significance to Biomedical Research and to the Program of the Institute: The development and evaluation of safe stimulating techniques for use in neural prostheses are major goals of the Neural Prosthesis Program of the Institute.

Proposed Course of Contract: This contract terminated in June 1979.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF CALIFORNIA, LOS ANGELES (N01-NS-4-2331)

Title: Studies on the Effects of Electrostimulation of the Cerebellum

Contractor's Project Director: Thomas Babb, Ph.D.

Current Annual Level of Support: \$145,700

Objectives: The effects of cerebellar stimulation on the electrical and behavioral aspects of seizures produced by alumina cream implants in the hippocampus of monkeys and on the firing behavior of hippocampal single units are being studied.

Major Findings: 1. In a single monkey, there was a significant reduction in clinically observable seizures attributable to midbrain raphe stimulation. However, subclinical EEG seizures were not significantly reduced. Neither subclinical or clinical seizure durations were affected by raphe stimulation in this animal. 2. Stimulation of monkey cerebellum for 1,080 hours at 14.7 microcoulombs/cm² results in less cerebellar cortical damage than stimulation at 35 microcoulombs/cm² for 205 hours. 3. Experiments in rat demonstrated that cells of the subiculum as well as hippocampal neurons are inhibited by stimulation of the fornix.

Significance to Biomedical Research and to the Program of the Institute: These studies should provide information on the mechanisms, if any, by which cerebellar stimulation modifies clinical seizures and movement disorders. Studies of midbrain and brainstem inhibitory projections to the hippocampus may provide pathways for control of temporal lobe seizures.

Proposed Course of Contract: This contract is completing its final year and will be terminated in June 1980.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF MINNESOTA (N01-NS-4-2332)

Title: Study of the Effects of Electrical Stimulation of the Cerebellum

Contractor's Project Director: Dr. James Bloedel

Current Annual Level of Support: \$89,290

Objectives: The effects of cerebellar stimulation on primate models of spasticity and movement disorders are being evaluated. The neurophysiological mechanisms and anatomical pathways associated with such stimulation are being examined.

Major Findings: 1. Stimulation of the anterior lobe of the cerebellum in monkeys results in a reduced excitability of the monosynaptic reflex evoked from the gastrocnemius-soleus nerve. Increased stimulus current produced a greater suppression of the reflex and a slight rebound was observed following stimulation. 2. Stimulating the posterior lobe was found in some cases to produce an increase in the excitability of the monosynaptic reflex. 3. Stimulation of the anterior lobe had mixed effects on polysynaptic segmental reflexes. For example, the excitability of the shorter latency (I) component was increased at 100 Hz while the second component (II) was reduced. 4. Stimulation of the surface of the cerebellum in monkeys with experimentally induced spasticity was studied. Reflexes, elicited by passive limb displacement of either the triceps or the biceps, were increased in magnitude during periods of cerebellar stimulation compared with non-stimulated control periods. Similarly, resting baseline EMG of both biceps and triceps increased during cerebellar stimulation.

Significance to Biomedical Research and to the Program of the Institute: These studies should provide information on the neurophysiological mechanisms, if any, by which cerebellar stimulation modifies normal movement and movement disorders.

Proposed Course of Contract: An animal model of spasticity based on cortical ablation has been developed and the effects of cerebellar stimulation in various locations and at various stimulus levels will be quantitatively evaluated in this animal model.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: STANFORD UNIVERSITY (N01-NS-5-2306)

Title: Transdermal Stimulation Electronics for Auditory Prostheses

Contractor's Project Director: Robert White, Ph.D.

Current Annual Level of Support: \$137,328

Objectives: Design and development of transdermal stimulators to be used in the evaluation of multichannel cochlear implant auditory prostheses.

Major Findings: 1. A titanium hermetic package has been designed and is presently being evaluated. 2. Prototype, 12-channel transdermal stimulators have been constructed and are undergoing testing. This system uses all custom designed, integrated circuit electronics and achieves its functions using six integrated circuit chips. 3. A 12-channel stimulation system has been designed and built for evaluating not only the present system but more advanced future systems.

Significance to Biomedical Research and to the Program of the Institute: The Institute is presently supporting under the grant mechanism the evaluation of multichannel auditory prostheses. This contract will provide electronic stimulators to several of these grantees.

Proposed Course of Contract: The 12-channel system will be modified to use radio frequency links for both signal transmission and power transmission. The 12-channel system must undergo long-term in vitro and animal in vivo testing before being supplied to grantees for human implantation.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NEUROSCIENCES
RESEARCH PROGRAM (NRP) (N01-NS-6-2343)

Title: Support of the Neurosciences Research Program

Contractor's Project Director: Frederic G. Worden, M.D.

Current Annual Level of Support: \$343,000

Objectives: The objectives of this contract are to examine current data and concepts of brain structure and behavior at all levels of complexity and to accelerate progress on crucial problems of neural science.

Major Findings: Work sessions held during the year, with the names of the chairpersons in parentheses, were as follows:

The Role of Peptides in Behavior (J.C. Liebeskind)

Perspectives on Research in Neurogenetics (S. Benzer, R.L. Sidman, and J. Hall)

Dynamics of the Brain Cell Microenvironment (Charles Nicholson)

Cerebral Cortex (H.H. Jasper and B.A. Milner)

The Role of Fast Transport in the Nervous System (H. Thoenen and G.W. Kreutzberg)

Human Cognitive Waves: What They Do and Do Not Tell About Brain Function (R. Galambos and S.A. Hillyard)

The results of each of these conferences have been or will soon be published in book form as part of the Neurosciences Research Program Bulletin. Each conference will be published as a separate volume.

In addition to the planning sessions for each of these conferences, planning sessions also have been held during this year for future conferences, one of which will be on the subject of Neuronal Fibrous Proteins.

During this contract period there were two Stated Meetings of the Associates of the Neurosciences Research Program. The first was held in October 1978. A large part of it was devoted to preparation of the five-day Work Session on Cerebral Cortex. In addition, there were inaugural addresses by the newly elected Associates; Ann M. Graybiel, of the Massachusetts Institute of Technology, John J. Hopfield of Princeton University, Richard M. Held of the Massachusetts Institute of Technology, and Hans Thoenen of the Max Planck Institute for Biochemistry of Munich. The 37th Stated Meeting of the Associates was held in March 1979. Valedictory talks were given by Manfred Eigen and Werner E. Reichardt, departing Associates. Eigen, a physicist

who won the Nobel Prize in chemistry, spoke on the evolution of molecules in a talk entitled "T-RNA: A Primordial Gene?" Reichardt's title was "How is Information Selectively Destroyed?" and dealt with a system's approach to information transfer, storage, and elimination in the nervous system. There were also presentations by Rudolfo Llinas on "Theoretical Approaches to Distributed Properties of the Central Nervous System" and by his colleagues A. Pellionisz on "Tensorial Modeling and Computer Simulation of Distributed Nerve Net Properties."

The F.O. Schmitt Medal and Lectureship was awarded to Dr. Stephen W. Kuffler of Harvard University. His public lecture was entitled "Synaptic Transmission: In Search of Models", and will be published as a supplement to the NRP Bulletin. The prize and medal were provided by a contribution from a private source to the Neurosciences Research Foundation. The prize had a monetary value of \$2,500.

The M.I.T. Graduate "Seminar in Neuroscience Research Topics" had four students this year, who attended all NRP Work Sessions, Stated Meetings and Conferences. The students are required to participate in reviews of work sessions with NRP staff and work session chairpersons. Each student prepares a written proposal for a possible Work Session which in his opinion would define a growing point in neuroscience. He outlines the scope of the topic, the issues around which it would be organized, and a list of scientists who have contributed importantly to the subject area, thus having intimate contact with all aspects of the NRP.

This year three new members were elected as Associates: Tomas Poggio of the Max Planck Institute for Biological Cybernetics, Tuebingen, Germany; Richard L. Sidman, Harvard Medical School; and Charles F. Stevens of Yale University.

Significance to Biomedical Research and to the Program of the Institute: NRP endeavors to identify those research areas in the neurosciences which are ready for exploitation and which are most likely to yield important new concepts. This will help FNP to identify the most relevant areas of research for program initiatives.

Proposed Course of Contract: The activities of the NRP will be of the same kind as in previous years and of approximately the same scope. Individual research areas to be emphasized will be determined. However, in the coming Fiscal Year, NRP will be supported on a research grant basis rather than as a contract. After a site visit and peer review, following their application for a research grant, a high enough priority was given to their project to warrant funding by our Institute. Additional funding will be provided also by NIMH and possibly other Institutes. As in the past, they probably will receive funds also from private sources.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 - September 30, 1979

Contractor: McMASTER UNIVERSITY (N01-NS-6-2344)

Title: Neuroanatomical Asymmetry in the Human Temporal Lobes and Related Psychological Characteristics

Contractor's Project Director: Sandra F. Witelson, Ph.D.

Current Annual Level of Support: \$75,500

Objectives: Patients in good neurological and mental health at a cancer clinic are approached by a trained "clinical coordinator" about granting permission for autopsy and taking psychological tests. The tests are those known to be affected by lesions of the temporal lobe on the left or the right; variations in anatomical asymmetry in the two normal temporal lobes will be investigated for relationships to the test scores.

Major Findings: As of June, 46 patients signed informed consent forms, and 46 have undergone some psychological testing. Twenty-eight patients have died and 19 brains have been obtained. Gross anatomical measures have been made on most brains and quantitative histological procedures have begun on selected brains.

Significance to Biomedical Research and to the Program of the Institute: The research should help solve the mystery of why nearly a quarter of human brains do not show the temporal lobe asymmetry found in the two-thirds majority; the results should provide insight into the hemispheric specialization of the human brain.

Proposed Course of Contract: Testing of patients is planned until a total of 60 brains becomes available for gross measurements and eight specimens with extreme asymmetry (4 left and 4 right temporal areas larger) will have histological analyses. The prospect of obtaining a sufficient number of volunteers within the contract period is good. An extension of the contract will be necessary to complete the neuroanatomy; there are adequate funds in the contract to cover the proposed work.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: STANFORD UNIVERSITY (N01-NS-7-2366)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Robert White, Ph.D.

Current Annual Level of Support: \$134,000

Objectives: The electrical and mechanical properties of the eighth nerve as it passes through the modiolus are being modelled. The results of these studies will be used to design second generation multielectrode arrays for stimulation of the eighth nerve in the human modiolus.

Major Findings: 1. Tantalum-on-sapphire rigid modular prototype electrodes have been designed and fabricated. 2. Physiological experiments have demonstrated that the nerve populations stimulated by separate fine-wire microelectrode arrays in the eighth nerve have a high degree of independence, that is, essentially separate nerve populations are stimulated by the different electrodes.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve may provide a means of communication for sensory deaf individuals. The NINCDS is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This contract will lead to the development of electrode arrays suitable for human implantation in the modiolus as part of an auditory prosthesis for the deaf.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-7-2367)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Michael Merzenich, Ph.D.

Current Annual Level of Support: \$79,500

Objectives: The electrical and mechanical properties of the scala tympani are being modelled, and, on the basis of these studies, multichannel stimulation electrode arrays will be developed which are suitable for stimulation of the eighth nerve in humans.

Major Findings: 1. The optimum position for electrode contacts in scala tympani arrays has been studied. The position depends upon whether there are surviving eighth nerve dendrites. 2. Overstimulation studies to determine the safety of scala tympani stimulation have indicated that a 2 to 3-fold safety factor exists between the levels for effective stimulation and damage to the cochlea. 3. Studies to determine the effects of neural inactivity on the auditory nervous system indicate that changes incurred by inactivation can be reversed by reactivation of the auditory nerve by electrical stimulation. 4. Using human cadavers, some of the factors responsible for electrode array insertion trauma have been determined.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve in the scala tympani may provide a means of communication for sensory deaf individuals. This Institute is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This contract will lead to the development of multichannel electrodes suitable for implantation in the scala tympani of humans as part of an auditory prosthesis for the deaf.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: GINER, INC. (N01-NS-8-2300)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Harry Lerner, Ph.D.

Current Annual Level of Support: \$102,370

Objectives: Research on methods of increasing the charge storage capability per unit volume and the current density output capability of capacitor electrodes that are suitable for intracortical stimulation of neural tissue is being carried out. Prototype capacitor electrodes will be fabricated.

Major Findings: 1. Using an etching technique, conventional sintered capacitor slugs have been shaped into conical configurations with a maximum diameter of 200 microns. 2. Using a tantalum powder-glycerin slurry, tantalum electrodes have been formed on the tips of tantalum wires and the effects of various manufacturing variables have been studied. Charge storage per unit volume exceeding current commercial production values has been obtained in prototype electrodes.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of central nervous system tissue.

Proposed Course of Contract: The further development of capacitor technology and the production of prototype electrodes for use by other contractors in the Neural Prosthesis Program and other interested investigators will occur.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: EIC CORPORATION (N01-NS-8-2392)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: John McHardy, Ph.D.

Current Annual Level of Support: \$99,735

Objectives: Improvements in the charge storage capability per unit volume and the current density output capability of capacitor electrodes that are suitable for intracortical stimulation of neural tissue are the major objectives. Prototype capacitor electrodes will be fabricated and supplied to other investigators.

Major Findings: 1. Capacitor electrodes have been formed by plasma etching of tantalum wire. A maximum etch ratio of 1.6 was achieved which is too low to warrant further investigation of plasma etching. 2. Using electrolytic etching, typical etch ratios have been on the order of three. Ultrasonic agitation and a current density of at least 1 ma/mm² are required for reproducibly achieving large etch ratios. 3. Tantalum pentoxide layers have been prepared by plasma oxidation. Due to irregularities of the oxide layer, this method has been abandoned and replaced by anodic oxidation. 4. Constant voltage anodization forms a more uniform, low leakage oxide film than slow voltage ramp anodization. 5. Experimental electrodes have been produced utilizing electrophoretic tantalum powder deposition.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of central nervous system tissue.

Proposed Course of Contract: The further development of capacitor technology and the production of prototype electrodes for use by contractors in the Neural Prosthesis Program and other interested investigators will occur.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: UNIVERSITY OF MISSOURI (N01-NS-8-2393)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Allen Hahn, Ph.D.

Current Annual Level of Support: \$169,344

Objectives: Evaluation of available implant materials and development of new materials for possible use as implant encapsulants, sealants, and lead insulators.

Major Findings: 1. Three initial polymers have been formed by plasma polymerization. These are: tetrafluroethane, tetramethyldisiloxane, and methane.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved encapsulation and sealing systems to prevent their access to the implants will be useful not only to neural prostheses, but to all artificial organs that involve implanted electronics.

Proposed Course of Contract: This project is in its first year and the major effort has been devoted to acquiring and assembling the necessary equipment for forming and evaluating plasma discharge polymers. During the future, major effort will be placed on evaluation and development of new polymers as needed.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: CITY UNIVERSITY, LONDON (N01-NS-8-2394)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Dr. William Wake

Current Annual Level of Support: \$28,420

Objectives: This research is concentrating on methods of improving the adhesion of insulators to conductors and other insulators that are used as implant packages, encapsulants, sealants and lead insulators in implanted neural prostheses.

Major Findings: 1. Zisman's critical surface tension has been measured on several materials including alumina substrates supplied by Dr. Brindley's Visual Prosthesis Unit. The surface energy was found to be much lower than predicted and further evaluation disclosed that the alumina contained about 5% glass. This results in the surface being essentially glassy in nature and causes poor adhesion of silicone materials. 2. Lap joints of Dow-Corning 3140 and alumina ceramic have been tested for strength as a function of duration of water immersion. After 34 days of soaking, there is little change in joint strength.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved sealing systems to prevent their access to the implants will be useful not only to neural prostheses, but to all artificial organs that involve implanted electronics.

Proposed Course of Contract: This project is in its first year and is in the process of acquiring the necessary equipment and materials. It is anticipated that adhesion of various insulators to tantalum pentoxide will be initiated in the coming year.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1978 through September 30, 1979

Contractor: ELECTROCHEMICAL TECHNOLOGY CORPORATION (NO1 NS 0-2316)

Title: Electrochemical Studies

Contractor's Project Director: Dr. Theodore Beck

Current Annual Level of Support: (This contract was being negotiated during July 1979).

Objectives: Study of the electrochemical reactions that accompany electrical stimulation of the nervous system and development of new electrodes based on ion selective membranes.

Major Findings: Not applicable.

Significance to Biomedical Research and to the Program of the Institute: Neural prostheses that utilize functional electrical stimulation require safe techniques for neuronal activation and inhibition. This work will provide a better understanding of the electrochemical factors involved.

Proposed Course of Contract: This contract is just beginning so the proposed course is essentially the pursuit of the "Objectives".



ANNUAL REPORT

October 1, 1978 through September 30, 1979

Neurological Disorders Program

National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
October 1, 1978 - September 30, 1979

NEUROLOGICAL DISORDERS PROGRAM
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
NATIONAL INSTITUTES OF HEALTH

The Neurological Disorders Program supports research in the neurological disorders of early life, convulsive and other paroxysmal disorders, neurological disorders of adult life, neuromuscular disorders, demyelinating and sclerosing disorders and the infectious diseases of the nervous system. The program supports 610 research grants, including both fundamental and clinical research program projects devoted to neurological disorders. Directed research activities were supported by 4 research contracts in the Developmental Neurology Branch and by 13 research contracts in the Epilepsy Branch. These include 5 Comprehensive Epilepsy Programs, three of which will be recompeting for research support under the grant mechanism in 1980.

During 1979, NDP received 400 approved applications for research support. The apparent decline in the number of applications received is due to a number of factors: 1) a better funding rate in 1978 reduced the number of amended applications received, and 2) redefinition of assignment codes for programs within the institute resulted in some changes. To this date, 234 awards have been made. Thus, we have been able to continue the momentum initiated in 1978 and to provide support for more than half of the scientifically meritorious applications received. There are areas in which we need to stimulate greater research activities. A by no means exhaustive list would include neurobiological studies of autism, amyotrophic lateral sclerosis, and the dementias of adult life.

Over the past year the Program has been involved in implementation of the recommendations of the Epilepsy and Huntington's Disease Commissions. Applications for both an Urban Comprehensive Epilepsy Center and an Huntington's Disease "Centre Without Walls" are currently under review for award in FY '80. Further details of these efforts are found in later sections. Program staff participated actively in the deliberations leading to the formulation of the Institute's National Research Strategy and will be involved in implementation of the pertinent goals developed therein.

ADMINISTRATIVE

Budget

The Neurological Disorders Program has been allocated a total of 65.8 million dollars in Fiscal Year 1979 to support its varied research programs through research grants, contracts and direct operations mechanisms. This funding level has been sufficient to support all of NDP's ongoing research programs and to fund a modest number of new initiatives. However, these funds were not sufficient to mount major research efforts to implement all of the recommendations of the Epilepsy and Huntington's Disease Commissions which are under the purview of the NDP. As a consequence, these efforts must necessarily be delayed until sufficient funds become available. It was

estimated in NDP's FY-79 implementation plan that 91.5 million dollars would be required to fund fully ongoing, as well as new, research efforts including all of the recommendations of the two Commissions.

NDP's budget allocation for FY-79 includes a ceiling of \$90,000 for travel expenditures during the fiscal year. This represents a \$2,000 increase over our FY-78 ceiling which provided some funds for support of travel needs generated by the two Commissions. While the FY-79 ceiling is not ideal and has required a substantial curtailment in NDP's meeting travel expenditures this amount appears adequate to allow the minimum level of research grant and contract surveillance, and to provide a beginning in implementation of Commission recommendations.

The NDP's budget permanent full-time employment ceiling for FY-79 totals 82 positions. This represents a reduction of 5 positions in NDP's FY-78 employment ceiling. This reduction has severely hampered our efforts to staff the program adequately and to obtain the necessary expertise required to pursue effectively research objectives of the Program and the Institute. This is particularly true in areas of the recently reorganized Developmental Neurology Branch where major new research initiatives are being undertaken and specialized expertise is required which is not available among current staff. Efforts are now underway to alleviate temporarily the problems created by our reduced employment ceiling by gaining access to required specialized expertise through the use of the NIH Special Expert Authority. This authority allows for the appointment of individuals with highly specialized expertise through ceiling exempt time limited appointments. This authority will also be utilized during FY-79 to provide staffing support to allow continuation of Drug Development activities in the Epilepsy Branch, NDP.

Personnel

The reorganization of the DNB to reflect a change in research initiatives resulted in several employees within the Branch with specialized expertise becoming excess to the personnel needs of the program. Of these employees, two have been successfully placed in other program areas of the Institute, three have retired and earnest efforts are now underway to locate comparable positions for the remaining three employees elsewhere in the Institute and/or the NIH.

Appointments

Dr. J. Kiffin Penry, Director, NDP, NINCDS, retired from government service on June 30, 1979. Dr. Penry had a long and distinguished government career spanning more than 20 years. During this time his research accomplishments received worldwide recognition and acclaim and have served as models in the area of research involving the various disciplines of the neurological disorders.

Dr. Floyd J. Brinley, Jr. has been appointed to replace Dr. Penry as Director, NDP, NINCDS. Dr. Brinley will enter on duty through the Public Health Service Commissioned Corps on July 15, 1979.

Dr. Penry also served as Chief, Epilepsy Branch, NDP, NINCDS. Dr. Roger J. Porter has been appointed to serve in an acting capacity in this position until a successor to Dr. Penry can be identified.

Dr. Katherine L. Bick was appointed to the position of Deputy Director, NDP, NINCDS, on June 3, 1979. In this capacity she will be responsible for assisting the Director, NDP, in planning, implementing and evaluating varied NDP extramural and collaborative research programs supported through research grants and contracts.

Dr. Emanuel Stadlan was appointed to the position of Medical Officer in the NDP on July 1, 1979. Dr. Stadlan will be responsible for planning, initiating and evaluating a comprehensive research program designed to determine the etiology of demyelinating and sclerosing disorders and to develop methods of early diagnosis, treatment, prevention and cure of these disorders.

Space

The Director, NINCDS recently initiated substantial space reassignments to program areas housed in the Federal Building. Because of these space reassignments the NDP will not be able to house the staff and facilities of the Epilepsy Branch in contiguous space on the first floor of the Federal Building. Plans have already been submitted to effect the necessary relocation.

Awards/Promotions

The NDP continues to be a major recipient of services provided by loyal, dedicated and conscientious federal employees assigned to the program. Thus far this fiscal year, three employees have been rewarded for outstanding performances through issuances of quality step increases and three employees have received promotions. The program anticipates severe difficulties in position classification during the remainder of FY-79 because of the requirement to reclassify clerical support positions and to rewrite position descriptions of affected employees in the Factor Evaluation Format. The classification standards for these positions have been revised and it is anticipated that a substantial number of employees will be adversely affected by the applications of these new standards. In addition, the application of these new standards will preclude the advancement of several highly efficient clerical employees who have willingly assumed additional responsibilities in support of the various activities of the program. This insensitivity of the personnel process to program needs for attracting, developing and maintaining superior individuals who will work to achieve program goals, provides continuing frustrations for government managers.

CONTRACT NARRATIVE
Neurological Disorders Program
October 1, 1978 - September 30, 1979

CLINICAL NEUROLOGY INFORMATION CENTER AT THE UNIVERSITY OF NEBRASKA
(NIH-NINCDS-72-2300)

Title: The Operation of a Clinical Neurology Information Center

Contractor's Project Director: Walter J. Friedlander, M.D.

Current Annual Level of Funding: \$160,000

Objectives: To operate a specialized Information Center on Clinical Neurology. This Center will be an international focal point for information relating to those diseases of interest to NINCDS, especially information relating to diagnosis, treatment and prevention of diseases of the brain and central nervous system. The Center is producing reviews of various clinical problems of interest to the Government, bringing together the relevant clinical knowledge as it applies to the problem. These reviews may focus on an entire disease problem as a whole, or on any distinct part of a disease entity. The Center will identify sources of information relevant to clinical neurological problems, including indexing services, abstracting services, periodical journals, books, monographs, etc.

Major Accomplishments: The Center's most innovative product and one that has been received enthusiastically by the approximately 1200 scientists who receive it is the Concise Clinical Neurology Review. This publication emphasizes a one sentence (terse) abstract of each paper in a cluster of terse statements on a single topic. A number of these topics are covered in a single issue of the bulletin. The bibliographic citations are referenced by a number and appear together in a second part of the bulletin. Approximately 375 papers are selected for inclusion each month, based on a review of 940 serials. This publication seems to fulfill a need not otherwise met in neurology. It is produced once every two weeks and has a subscription rate of \$28 per year.

Proposed Course of the Contract: This program is under the surveillance of an NINCDS project officer and its performance is under continued review.

Disorders of Early Life
and
Other Neurological Disorders

This program covers several neurological areas pertaining primarily to the developmental, sensory and metabolic aspects of the nervous system. Statistically this program supports 256 research projects, active as of July 1, 1979, with a total investment of about 19 million dollars. In fiscal year 1978, a total number of 191 competing research grant applications were assigned to this program. Of these 95 were funded giving a funding ratio of 1:2.

Developmental program is directed toward understanding the normal neurological events in the development of CNS and the effects of internal and/or external stimuli, stresses, or organic factors which influence these normal sequences. Also, the following broad areas of research are covered under this program: Vitamins - Role of thiamine in brain disorders, folic acid deficiency and brain development; Nerve Growth Factor - Isolation, characterization, and functions of NGF, role of NGF in neuronal differentiation and regeneration; CSF and Hydrocephalus - CSF formation and absorption in hydrocephalus, pathogenesis of hydrocephalus, role of choroid plexus in regulation of CSF; Synaptology - Synaptic transmission, synaptic relations in sensory systems, synaptic connectivity in motor systems, nerve-muscle synapse, nervous system development and synapse formation; Cell Surface Events - Cell adhesion and contact, effect of lectin-like protein on cell recognition; Membrane - Membrane connections and drug action, cell interconnection and transport across membranes.

Sensory Modalities include studies on spinal somesthetic pathways, sensory properties of electrical brain stimulation, neural control of ingestive behavior, development of perceptual capacities, etc. Pain and related aspects comprise a considerable portion of this program. For example, effects of local and general anesthesia are being investigated at the sub-cellular level with respect to membrane conductivity, permeability and transport. Also included in this are the studies of hemispheric specialization of cognitive mode, laterality of handedness, motor function, attention and learning, state-dependent control of somatic reflex activity, neuronal control of discrete behavioral processes, etc.

Learning and Memory: One of the most intriguing and challenging areas of research involving the nervous system is the way information is received, stored, transferred and retrieved, either on short term or long term basis. Mainly two lines of attack have been proposed. One involves spread of learning from one brain region (hemisphere) to another region as detected by neurophysiological stimulation and recording methods and delineation of factors that influence the direction of EEG asymmetry in perception and learning. The second mode of attack involves biochemical approaches. During the past few years evidence has been presented suggesting that catecholamines are significantly involved in memory processes. There is some indication that experimentally induced amnesias can be reversed by

manipulation of catecholamine systems which may have some potential for treatment of the various amnesic states in man. Also, closely related to this approach is a demonstration that certain proteins have a critical role in the functional mechanisms of learning and retention of information. A current hypothesis is that proteins may have neurosecretory function in the brain. In clinical terms, the results might suggest that certain types of senile dementias, mental retardation and chronic alcoholism, where there is memory loss, may arise from a decrease in the capacity of the CNS to make specific proteins. As indicated above, electrophysiological and biochemical approaches are being used but thus far have added little to our understanding of basic mechanisms in man. Intensive investigation exploiting these and other approaches is underway.

Inherent and induced metabolic disorders: Lysosomal storage diseases are emerging as an important and rapidly expanding group of inherited human disorders of metabolism. Most of these diseases have progressive nervous system deterioration as their major component. Onset of neurological signs in these disorders ranges from infancy to adult life, and all are severely disabling or fatal diseases. Data on population genetics and incidence are fragmentary due to the recent discovery of most of these diseases and because biochemical methodology needed to differentiate between clinical subtypes has only become available within the past few years. The insidious nature of this pattern of inheritance permits the carrier genotype to become widespread in a population before recessive patients appear in significant numbers. The benefits and limitations of screening, prenatal diagnosis and selective abortion for prevention of these diseases are apparent. Progress in therapy of the lysosomal diseases has become rapid. Results from patient trials have provided encouragement and sufficient justification for mounting an intensive effort in the development of safe and effective methods for treatment of these diseases. This program supports fundamental as well as clinical research on lipid and other inherited diseases. Some of these diseases are: Nieman-Pick, Gaucher's, Krabbe's, Fabry's, metachromatic leukodystrophy, etc. Gangliosidoses (e.g., GM1, GM2, GM3) form an integral part of this research area. A detailed report on Lysosomal Storage Diseases follows. Also included in this program are related areas pertaining to myelin, cholesterol, phospholipids, keto and hydroxy fatty acid metabolism.

Reye's syndrome is primarily a disorder of childhood, the age of those affected ranging from a few months to adolescence. Epidemiologically, two groups of cases can be defined: Those cases which occur in older children (median age of 11 years) cluster in time and geographic region, and are associated with antecedent influenza infections. The other group of cases, those which occur sporadically throughout the year, are isolated in occurrence, in younger children (median age of 6 years) and are associated with a wide variety of antecedent viral illnesses. A detailed report on Reye's syndrome research supported by this program is included.

Malnutrition and Toxic Substances: There is strong evidence that nutritional and environmental entities cause encephalopathy which are probably

the results of damage to the CNS. These studies are concerned with morphological and biochemical changes in isolated microcirculatory fractions in these disorders.

Neuroendocrine Disorders: Studies are being conducted on the influence of thyroid hormones on developing brain with the ultimate aim of understanding mental retardation occurring in hypothyroid conditions. The effects of neonatally administered glucocorticoids and thyroxine on postnatal cell formation are being examined since both treatments lead to cell deficits in developing brain.

Lysosomal Inherited Storage Diseases

Introduction

Lysosomal storage diseases are emerging as an important and rapidly expanding group of inherited human disorders of metabolism. Most of these diseases have progressive nervous system deterioration as their major component. Onset of neurological signs in these disorders ranges from infancy to adult life, and all are severely disabling or fatal diseases. Data on population genetics and incidence are fragmentary due to the recent discovery of most of these diseases and because biochemical methodology needed to differentiate between clinical subtypes has only become available within the past few years. The most reliable information of this type comes from studies of Tay-Sach's disease. Data from mass screening programs and projections based on birth of diseased children agree closely and place the carrier frequency of this disease among Ashkenazi Jews at 1 in 30. Of greater significance to the U.S. population as a whole is that while only 30 percent of patients with this disease are non-Jews, current estimates predict that between 500,000 and 800,000 Jews and non-Jews living in the United States are carriers of this disease. World figures are projected to be 5-7 times this number. These figures are remarkable but not entirely unexpected since this disorder, and apparently most lysosomal diseases, are inherited as autosomal recessive traits. The insidious nature of this pattern of inheritance permits the carrier genotype to become widespread in a population before recessive patients appear in significant numbers.

The benefits and limitations of screening, prenatal diagnosis and selective abortion for prevention of these diseases are apparent. Progress in therapy of the lysosomal diseases has reached a pivotal juncture. Results from patient trials have provided encouragement and sufficient justification for mounting an intensive effort in the development of safe and effective methods for treatment of these diseases.

Although much remains to be learned about the pathogenesis of lysosomal enzyme deficiency diseases, current knowledge is sufficiently advanced to warrant focusing increased attention and effort on the final and most important phase in the evolution of research on these diseases; enzyme replacement therapy. Results of in vitro tissue culture studies and preliminary in vivo trials in man and animals encourage the notion that exogenous lysosomal hydrolase administered parenterally can be taken up and utilized by enzyme deficient tissues to correct a metabolic defect. While this experience justifies optimism and encourages continued pursuit of promising replacement therapy, several fundamental questions must be answered and certain technical hurdles surmounted before this goal can be fully achieved.

Specific storage diseases are discussed below:

Niemann-Pick Disease

Niemann-Pick disease is an inheritable lipid storage disease generally characterized by the tissue accumulation of sphingomyelin and believed to be due to deficiency of the enzyme sphingomyelinase. However, the disease is actually quite heterogeneous and at least five phenotypes have been suggested. In addition to sphingomyelin, bis-(monacylglyceryl) phosphate, bis-(MAG)P, an acidic phospholipid normally present in only trace amounts, has been reported to accumulate in some cases of Niemann-Pick disease. Furthermore, there have been a number of reports of patients with lipid storage disease, some resembling Niemann-Pick phenotypes, in which bis-(MAG)P concentration was greatly increased but in which sphingomyelin levels were normal or only slightly increased. These studies strongly suggest that the tissue accumulation of bis-(MAG)P may be related to human disease.

The accumulation of an acidic phospholipid has been identified as bis-(MAG)P in the livers of some patients with classical Niemann-Pick disease (Crocker Type A), in patients with "uncertain diagnosis" (early death, neurologic involvement with storage cells resembling a lipidosis), in a patient with "adult Niemann-Pick disease" (Crocker Type C, D or E) in which sphingomyelin levels were normal, and in a patient with late infantile amaurotic familial idiocy. Accumulation of bis(MAG)P has been reported in a patient with hyperlipidemia associated with hepatosplenomegaly and lipid storage cells in lymph nodes, liver and spleen. Although this case resembled Niemann-Pick disease clinically in some aspects, liver sphingomyelin levels were normal. Liver bis-(MAG)P elevation with intermediate levels of sphingomyelin and sphingomyelinase was recently reported in another case of adult Niemann-Pick disease. Finally, human "Niemann-Pick-like syndrome" has been induced by the coronary vasodilator, 4,4'-diethyl-aminoethoxyhexestrol, in which bis(MAG)P accumulates in liver, spleen, muscle and lymph nodes. This disease could be reproduced in rats by feeding 4,4"-diethylaminoethoxyhexestrol.

In the past few years much additional progress has been made in understanding the biochemical basis for some of the Niemann-Pick lipidoses, especially Types A and B. However, the nature of the defect in types C, D and E is still undetermined; sphingomyelin metabolism is apparently relatively normal in these cases. Bis-(MAG)P metabolism may be the abnormality of pathophysiologic importance in these diseases. Studies are being conducted to elucidate the relationship between disordered bis-(MAG)P metabolism and the pathophysiology of Niemann-Pick disease(s) as well as some unclassified lipidoses. Finally, phospholipids are important structural components of biomembranes and are important in the integrity and proper function of many membrane-bound enzymes, and although lipidoses of the kind described above are rather rare, it is probable that work on the biosynthetic and catabolic pathway of phospholipids will have a more general significance in terms of the biogenesis and properties of biomembranes.

Interaction of enzymes with lipid substrates: Since lipids are water insoluble, their interaction with enzymes is a phenomenon of heterogenous catalysis resulting from the fact that the true substrate is not a molecule of the lipid but a colloidal dispersion. The nature of dispersion depends upon the type of lipid and the method used. Prenatal or postnatal diagnosis of the lipidoses is becoming more widespread, but the existence of variants of the diseases and interfering factors while assaying the enzyme in reliable diagnosis are not recognized. This is especially true when lipid substrates are used. Conflicting data were reported on the nature of the enzymatic defect of a disease, e.g., on the utilization of lactosyl ceramide in Krabbe's disease. This disease was erroneously identified as lactosyl-ceramidosis and was proposed as a new disease. It is common experience that enzymatic reactions in which the substrate is a lipid frequently yield unreliable and irreproducible data. Currently, water-soluble, synthetic substrates are employed in diagnosis of lipid storage diseases with result that unreliable data are obtained. To mention a few problems: the physical state of the water-insoluble substrate, the membranous structure of the enzyme, the presence of non-specific absorption of the substrate or the enzyme.

Because of the difficulty in working with water-insoluble substrates, the pre- or postnatal diagnosis of the lipidoses is done with artificial, synthetic water-soluble substrates. However, several diseases cannot be diagnosed this way (e.g., Niemann-Pick's disease). Furthermore, this procedure might lead to the selection of wrong isoenzymes which happen to have a high affinity to the synthetic substrates. Such an erroneous selection of a wrong enzyme may be a matter of the life or death for an embryo or infant suspected of having a lipidosis. It is therefore imperative that a thorough understanding of the nature of the interaction of enzymes with lipid substrates be acquired in these diseases. It is precisely this approach to which a considerable part of research efforts is being directed. This approach has already yielded a significant contribution to the theoretical as well as the methodological aspects of lipid enzymology.

Gaucher's Disease

Gaucher's disease is characterized by the accumulation of glucocerebroside primarily in spleen, liver and bone marrow, and is due to a defect in the lysosomal enzyme, B-glucosidase, which is responsible for cleaving terminal glucose molecule from glucocerebroside. The disease is transmitted as an autosomal recessive trait and follows Mendelian inheritance pattern. Three forms of Gaucher's disease have been identified; infantile, juvenile and adult. The deficiency of enzymatic activity corroborates with increasing age of onset of the disease, i.e., lowest in infantile increasing to about 50% of normal control in the adult form. Although primary effect is in lipid metabolism, except in infantile form, CNS involvement is not clear. Enzymes involved in glucocerebroside metabolism have been identified and characterized with respect to properties, developmental changes in rat brain, and distribution among cell types and organs. Assay procedures were developed for these enzymes, involving whole tissue and natural substrates.

Many new compounds, resembling the natural substrates of these enzymes or the products of enzyme action, were synthesized and tested for their effects on the enzymatic rate. Several of these compounds acted as abnormal substrates for glucocerebrosidase (and galactocerebrosidase synthesis). A number of these compounds proved to be good inhibitors, either competitive or noncompetitive. Some of the synthetic compounds show promise for inducing disorders in animals that resemble the natural human genetic disorders, Gaucher and Krabbe disease. Others offer promise in the amelioration of these diseases.

Enzyme replacement therapy: It has been suggested that the glucocerebrosidase deficiency characteristic of this particular disorder may be amenable to treatment through supplementation with concentrated doses of purified normal enzyme. This approach seemed particularly appealing since involvement of the nervous system often does not occur and because the majority of the immobilized lipid is deposited within the reticulo-endothelial system where exogenous enzyme might be expected to be localized. The successful isolation of glucocerebrosidase from human placental tissue provided the opportunity for initiating these studies. The enzyme was infused into two patients with Gaucher's disease and a dramatic clearance of glucocerebrosidase from the liver as well as the circulation was observed.

An examination of the lipid levels in these same patients several months following enzyme infusion revealed the levels of glucocerebrosidase in blood were still substantially below the preinfusion level a year after it was administered. This provides a hypothetical "long term" model of lipid accumulation in Gaucher's disease. These considerations at the molecular level provide added encouragement for further investigation of enzyme replacement in hereditary inborn errors of metabolism.

Future studies: Characterize the purified enzyme in terms of properties. Examine the nature of the bond with substrate and activating materials, such as bile salts, emulsifier, and helper-proteins. Look for activated and inactive enzyme forms. Look for naturally occurring activators and inhibitors, including helper-proteins. Use of the purified enzyme to make antibodies. Label the antibody with an electron-dense material and locate the enzyme within cells by electron microscopy. Use the antibody to determine the reason of low enzyme activity in Gaucher's disease. Try to develop a large-scale isolation method for enzyme particularly from human urine or tissue, and see if it can be used in the treatment of Gaucher's disease.

Metachromatic Leukodystrophy (MLD)

Pathology of Metachromatic Leukodystrophy: The first indication of a biological role for an arylsulfatase was observed with a deficiency of arylsulfatase A in tissue of patients with metachromatic leukodystrophy (MLD). MLD is a genetically determined disorder characterized by accumulation of cerebroside

sulfate (sulfatide), particularly in the nervous system, which results in progressive neurological degeneration. Although the sulfolipid is a carbohydrate linked sulfate ester rather than arylsulfatase, a cerebroside sulfatase role for arylsulfatase A was implied. It was shown that purified porcine kidney arylsulfatase A did indeed have cerebroside sulfate sulfohydrolase activity. It was also demonstrated that extracts of tissues from MLD patients were unable to hydrolyze cerebroside sulfate. In order to elicit sulfatidase activity by the normal enzyme, it was necessary to supplement it with a heat stable complementary factor. Thus the requirements for the hydrolysis of the physiological substrate appeared to be more complex than those for synthetic substrates.

Forms of MLD: Actually MLD is not a single genetic disease; a variety of mutant enzyme forms associated with this disease have been shown. For example, MLD is arbitrarily divided into three classical forms: (late infantile, juvenile, and adult) differentiated by the age of onset of clinical symptoms. While it is difficult to clearly show any reliable level of arylsulfatase A in tissues or cultured cell extracts with most cases of MLD, it seemed unlikely that enzyme activity could be totally lacking in all forms of the disease. By a test system utilizing intact tissue culture cells, it has been demonstrated that cells derived from patients with later stages of the disease retain cerebroside sulfate hydrolyzing capability. In fact, the level of activity in this system was directly correlated with the age of onset of clinical symptoms. In general, an enzyme deficiency state could be due to decreased normal enzyme production, increased degradation, or the formation of a mutant form. By utilizing antibodies against normal human arylsulfatase A, it has been possible to show that a mutant enzyme protein is in fact present in cultured MLD cells and MLD tissue. While there is less antibody reactive protein in MLD cells than in normal, it is considerably more abundant than anticipated from residual enzyme activity alone. In fact evidence has been presented for antigenically active material in tissues even from late infantile MLD patients where essentially no residual enzyme activity can be detected.

Other conditions showing an arylsulfatase A deficiency have also been noted, such as multiple sulfatase deficiency disease and an atypical form of MLD. One patient's cells had 10% of normal enzyme when assayed with synthetic substrate, but no activity was found when assayed with cerebroside sulfate. It is thus apparent that not only a variety of mutant forms of human arylsulfatase A can be expected, but some may differ from the normal only in a subtle manner. A thorough characterization of the normal human arylsulfatase is therefore a necessary prelude to unraveling this complex system of human genetic defects.

Comparative characteristics of arylsulfatases A: Arylsulfatase A has been prepared from several animal tissues. It has also been purified from human sources. It was isolated at a high state of purity from placenta, however, the final product was exceedingly unstable and essentially no studies were performed on this purified enzyme. Very recently enzyme has been purified from urine. Comparative studies indicated that the activities of the enzymes from the three sources were essentially identical toward two synthetic substrates, 4-nitrocatechol sulfate and 4-methylumbelliferyl sulfate, and the physiological substrate, cerebroside sulfate. Observations on other properties

of human enzymes were similar to the ox enzyme. The amino acid composition of the human liver enzyme was similar to that of the ox enzyme in that proline content was unusually high, there was a preponderance of hydrophobic amino acids and there was an excess of acidic amino acids. The human enzymes have a pH of 4.7 compared to 3.4 for the ox enzyme so the excess of acidic amino acids was not as great in the human enzyme.

Studies with fibroblasts: Pioneering studies led to the identification of the metachromatic material in neural tissue as cerebroside sulfate, the deficient enzyme as arylsulfatase A, and the proof that this enzyme functioned as a cerebroside sulfate sulfohydrolase. Later, it was shown that the disease could be readily diagnosed by enzymatic assay of leukocytes. It was observed that cultured fibroblasts derived from a patient affected with late infantile MLD expressed the arylsulfatase A deficiency. The expression of the enzyme defect by cultured fibroblasts implied that MLD was amenable to prenatal diagnosis. Case reports of examination of five pregnancies at risk for MLD have appeared. At least four fetuses were found to be affected and termination of pregnancy was elected in each case.

Opinion is divided on whether leukocyte or fibroblast arylsulfatase A activity level is a reliable index of heterozygosity for MLD. The cumulative data on a statistical basis showed an activity ratio of 2:1:0 for control subjects, obligate heterozygotes and patients affected with MLD. This is consistent with a gene-dosage effect. However, in experimental set-up (leukocytes: 65, 7 and 4; fibroblasts: 34, 10 and 14) there was considerable overlap between the control and heterozygote groups, so that positive identification of the genotype of any isolated individual has been tenuous. Nevertheless, investigations carried out on several high risk families have shown clear segregation patterns within the family, so this approach may serve some utility. The greater difficulty in heterozygote diagnosis for MLD as compared with Tay-Sachs disease may be a reflection of the greater genetic heterogeneity involved.

Enzyme replacement therapy: Soon after the basic enzyme defect had been recognized, enzyme replacement therapy was tried in MLD patients. The treatments were ineffective, but there were a number of experimental limitations which are basically unavoidable with such trials. It was felt that it would be desirable to carry out preliminary feasibility studies in a controlled model system, and fibroblasts in culture offered such a system. A crude preparation of arylsulfatase A was isolated from human urine. MLD fibroblasts incorporated this enzyme added to the growth medium and retained activity for extended periods. When enzyme loaded cells were challenged with cerebroside sulfate, the pattern of incorporation and release of inorganic sulfate was identical to that of normal cells. Alternatively, if the cells were first allowed to accumulate cerebroside sulfate, then transferred to medium containing enzyme, the accumulated sulfatides were cleared. Thus, the feasibility of enzyme replacement at least in MLD fibroblasts, was established. While there is considerable distance between curing a flask of fibroblasts and a clinically effective therapy, the tissue culture model offers a valuable tool for basic testing.

Future investigations: The long term goals are to understand metachromatic leukodystrophy (MLD) at the molecular level. The enzyme deficient in this

genetic disorder is arylsulfatase A and an understanding of its physiological function(s), natural history, and physico-chemical properties is central to this goal. There is increasing evidence that there is a family of allelic mutations affecting this enzyme which in turn leads to a heterogeneity of clinical manifestations. Thus, the identification and characterization of the biochemical differences between the gene products is necessary before the relationship between biochemistry and pathology can be established. Findings from these studies will find utility in early type specific diagnosis, heterozygote identification, genetic counseling, antenatal diagnosis, and provide a rational basis for developing and testing specific approaches for therapeutic and/or prophylactic intervention.

Fabry's Disease

The metabolic defect in Fabry's disease is due to a lack of the enzyme, ceramide trihexosidase (alpha-galactosidase), which cleaves the galactosyl residue next to the terminal N-acetylgalactosamine residue in globoside. The result of this defect is accumulation of ceramide trihexoside, galactosyl-galactosyl-glucosyl-ceramide in visceral organs. Since the sequence of the saccharide chain isolated from Fabry's patients was shown to be galactosyl-galactosyl-glucosyl-ceramide, it is logical to assume that the defective enzyme in Fabry's patients is a galactosidase responsible for the hydrolysis of the terminal galactosyl residue in this glycolipid. The anomeric specificity of the galactosidase missing in Fabry's patients was not settled for a long time. In order to know its anomeric specificity, the anomeric configuration of the terminal galactosyl unit in ceramide trihexoside must be known. By using specific alpha-galactosidases, it has been proven unequivocally that the ceramide trihexoside isolated from the kidneys of Fabry's patients, normal human kidney, and other tissues contained terminal alpha-galactosyl linkages. Thus, basic biochemical studies on the alpha-and-B-galactosidases led to the correct understanding of biochemical etiology of Fabry's disease--the deficiency of a specific alpha-galactosidase. It should be pointed out that the substrate specificity of various glycosidases is far more complex than is generally realized. For example, several alpha-galactosidases isolated from various sources such as from Mortierella vinacea, Diplococcus pneumoniae, Calvatia Cyathiformis, and coffee beans, are active only in cleaving the terminal galactose present in the oligosaccharides of the raffinose family, but fail to cleave the terminal alpha-galactosyl residue from glycoproteins and glycolipids. Further studies showed that the alpha-galactosidase capable of hydrolyzing the terminal alpha-galactosyl residue in glycoproteins and glycolipids is the only one isolated from Fig Latex. Since this enzyme cleaves the terminal alpha-galactose from ceramide trihexoside very effectively, its potential use for enzyme replacement therapy in Fabry's disease is stressed.

Alpha-galactosidase isolated from human liver: Since alpha-galactosidase is the key enzyme which catabolizes ceramide trihexoside, alpha-galactosidase was prepared from human liver and placenta in highly purified form. This preparation showed 2 components, A & B. In order to elucidate the possible different physiological roles of the two isozymes, their substrate specificities were investigated. It has been reported that only alpha-galactosidase A can hydrolyze melibiose and ceramide trihexoside. In contrast with these reports, it was found that not only alpha-galactosidase A, but also B catalyzes

the hydrolysis of both ceramide trihexoside and melibiose. However hydrolysis of ceramide trihexoside by alpha-galactosidase A or B takes place only when the activator is added to the reaction mixture. With the same units of enzyme, the hydrolysis of ceramide trihexoside by alpha-galactosidase A proceeded at a faster rate than the reaction catalyzed by alpha-galactosidase B. The physiological role of alpha-galactosidase B is still obscure. Although it has been reported that Fabry's disease is due to the deficiency of alpha-galactosidase A, the role of alpha-galactosidase B remains to be clarified.

Activator requirement for glycosidases to hydrolyze glycolipids: It was found that highly purified alpha-galactosidase (or B-galactosidase) of human liver required the heat stable co-factor to hydrolyze ceramide trihexoside (or GM1 ganglioside) respectively. This activator is glycoprotein in nature. Chemical composition of activator indicated 17 amino acids, N-acetylgalactosamine, mannose, galactose, and N-acetylneuraminic acid (sialic acid). In order to develop a sensitive method for detecting the activator in various tissues, rabbits were immunized to produce the antibody against the activator. By using the immunological method, existence of the activator in various organs was determined. Since the activator has also been isolated from the liver, differences between the activator and the bile salts were examined. Results indicated that the activator and the bile salts are not related at all. This activator was also extracted from human kidney and brain. These findings on the activator requirement for the glycosidases to hydrolyze sphingoglycolipids have revealed new information about the complexity of the catabolism of sphingoglycolipids.

Glycolipids accumulated: Kidneys of patients with Fabry's disease accumulate both ceramide trihexoside; galactosyl-galactosyl-glucosyl-ceramide and ceramide digalactoside; galactosyl-galactosyl-ceramide. By using alpha-galactosidase isolated from Ficin, studies were made on the structure of ceramide digalactoside extracted from kidneys of a Fabry's patient. It was found that fig alpha-galactosidase liberates the terminal galactose from ceramide digalactoside whereas Jack bean alpha-galactosidase has no activity towards intact ceramide digalactoside. The results established the structure galactosyl-galactosyl-ceramide for this glycolipid. It is interesting to note that both glycolipids which accumulate in Fabry's disease have the terminal alpha-galactosyl residue. These results further support the biochemical etiology of Fabry's disease as being a deficiency of alpha-galactosidase.

Enzyme replacement therapy of Fabry's disease using tissue culture as a model: Fabry's disease is an X-linked inherited catabolic disorder characterized by the accumulation of large amounts of ceramide trihexoside and ceramide digalactoside. The structure of these two sphingoglycolipids has been established as described above. The biochemical abnormality of Fabry's disease is due to a genetic defect in alpha-galactosidase. Fibroblasts cultured from the skin of Fabry's patients exhibit both the chemical abnormality and enzymic deficiency and accumulated a 4- to 6- fold excess of ceramide trihexoside. To demonstrate the correction of this phenomenon, cells previously labeled with (C-14)-glucose were grown in a medium containing a highly purified alpha-galactosidase preparation obtained from Ficin. The results indicated that, in spite of its instability in culture, alpha-galactosidase was rapidly taken up from the medium by the cultured cells. Furthermore, it catabolized the stored ceramide

trihexoside in the cells. These findings support the reports of therapeutic endeavors by renal transplantation and plasma infusion in Fabry's disease and suggest the extension of such studies to other related disorders where the cultured skin fibroblasts are chemically abnormal, namely Gaucher's disease, Lactosyl ceramidosis, and GM2-gangliosidosis.

Future Investigations: To isolate homogeneous glycohydrolases from various sources, especially of those capable of hydrolyzing the sphingoglycolipids which accumulate in various types of sphingolipid storage disease; to characterize physical and chemical properties and the specificities of the enzymes toward various natural substrates; to isolate and characterize the glycoprotein activator from various tissues which stimulate the hydrolysis of sphingoglycolipids and to study its role in controlling the catabolism of sphingoglycolipids; to use glycosidases as a tool to study the structure of the complex carbohydrate chain in various sphingoglycolipids; to investigate the possibility of using glycohydrolases for enzyme replacement therapy in sphingolipid storage diseases.

Mannosidosis

Unlike most lysosomal storage diseases of humans, mannosidosis is relatively common disease of Angus cattle. In a population of 4 million cattle in New Zealand, it is estimated that about 10% are heterozygous carriers of this recessive trait. The disease is characterized by the storage of oligosaccharides containing N-acetylglucosamine and mannose in a repetitive sequence. The enzyme deficient is alpha-mannosidase which is unable to cleave the terminal mannose from stored oligosaccharides. The disease has been defined in pathological and biochemical terms as a basis to developing a control program in cattle and as a model for studying certain aspects of human storage disease.

Purification and study of acid alpha-mannosidase have indicated mol. wt. between 300,000 and 350,000. In plasma, it exists in a high mol. wt. either due to greater polymerization or a carrier molecule. Evidence is available that native alpha-mannosidase exists in a polymeric form and that the basic sub unit has a mol. wt. approx. 10,000. Complete purification has not yet been achieved.

Techniques for detecting cattle heterozygous for the mannosidosis genotype including factors affecting normal levels have been investigated. Plasma alpha-mannosidase levels are highly accurate in detecting heterozygotes. As age and environmental factors influence normal levels of enzyme, results of other individual tests are less accurate. Consequently, further experiments using leukocytes, lymphocytes utilizing reference enzymes are currently being evaluated. In heterozygous individuals, plasma and leukocyte enzyme levels are 37% those of normal individuals.

Basic work including the ultrastructural pathology of mannosidosis, tissue culture techniques and enzyme kinetics has been done as a prerequisite to experiments on enzyme replacement.

Enzyme replacement therapy by transplantation is being studied in an experiment involving a placental chimeric calf with mannosidosis born co-twin to a normal individual of opposite sex.

Future studies: To evaluate various techniques for identifying individuals heterozygous for a lysosomal enzyme deficiency. To purify acidic alpha-mannosidase and to study its molecular structure, various forms and properties. To study the storage product in mannosidosis and develop a quantitative test for use in enzyme replacement studies. To investigate some of the basic problems in enzyme replacement therapy using a stepwise experimental approach in expendable animals.

I-Cell Disease

I-Cell disease or mucopolipidosis II is a childhood disorder. The disease is believed to be transferred in an autosomal recessive manner and is characterized by a severe psychomotor retardation, early cessation of growth in stature, minimal skeletal deformities, mild or no hepatic enlargement, absence of excessive excretion of mucopolysaccharides in urine and the presence of numerous cytoplasmic granular inclusion bodies in cultured skin fibroblasts. Death occurs between the ages of two and nine.

Microscopic examination: Cultured fibroblasts derived from I-Cell patients contain abundant refractile cytoplasmic inclusions. These inclusions became an index for this disease and the object of extensive studies. Electron microscopy revealed that these inclusion bodies are composed of multivesicular membranes and display morphology similar to altered lysosomes. A small number of inclusion bodies were also observed in some fibroblast cells of fathers of affected children. Subsequent studies of liver, brain (i.e. neurons), peripheral nervous system (i.e. Schwann cells, axons), kidney and skin derived from I-Cell patients demonstrated the presence of inclusions similar to those found in cultured fibroblasts.

Chemical identification of the inclusions: These inclusions stain positive with periodic acid-Schiff reagent and Sudan Black. Extraction of the inclusions with chloroform: methanol prior to staining with Toluidine Blue results in a weak metachromatic product. These investigations suggested that the storage material may be both glycolipid and mucopolysaccharide. Lipid determinations on cultured fibroblasts revealed that I-Cell patients contained three-fold higher total lipid than control fibroblasts. This increase could not be attributed to any specific class or species of lipid. The relationship of the accumulation of lipid to the basic defect is even more puzzling since lipid contents of brain, liver and spleen from autopsied samples of I-Cell patients were within normal limits.

Identification of deficient enzymes in body tissues: Biochemical studies of I-Cell tissues and cultured fibroblasts are not in complete agreement. The most consistent finding to date is a marked decrease in the activity of B-D-galactosidase in autopsied samples of liver, brain, kidney and spleen obtained from I-Cell patients. For example, in liver the B-D-galactosidase activity was 8-25% of normal while the activity of the enzyme in gray matter was 25% of normal levels.

Enzymes in fibroblasts: In contrast to the results obtained with tissues, experiments using cultured fibroblasts demonstrated very low levels or virtual absence of B-D-galactosidase and alpha-L-fucosidase activities, while the activities of the N-acetyl-B-D-hexosaminidase, B-D-glucuronidase, arylsulfatase A, alpha-galactosidase and alpha-D-mannosidase were greatly reduced (5-25% of normal control values). In addition, B-D-glucosidase, acid phosphatase and B-D-xylosidase showed normal or slightly increased levels of activity in I-Cell cultured fibroblasts. Non-lysosomal enzymes such as lactic acid dehydrogenase and malic acid dehydrogenase were also at normal activity levels in I-Cell cultured fibroblasts. Mixing experiments employing fibroblasts or frozen tissues derived from I-Cell patients and control subjects resulted in intermediate levels of the affected enzyme activities. These data suggest that the reduced activities in the skin fibroblasts and tissue samples are not due to the presence of endogenous inhibitors.

Enzymes in culture medium: The supernatant medium from I-Cell cultured fibroblasts revealed two- to nine-fold increase in the extracellular levels of B-D-galactosidase and B-D-glucuronidase and appeared to be dependent on the type of medium used. B-D-galactosidase remained at normal levels in the supernatant media of I-Cells culture, while a 9-fold increase in specific activity occurred at 15 days after sub-culture.

Enzymes in body fluids: Increased levels of lysosomal hydrolase activities were found in the extra cellular fluids of I-Cell patients. Plasma contained increased enzyme levels which varied from two- to 90-fold depending on the enzyme in question (e. g. arylsulfatase A activity was increased 90-fold). Cerebrospinal fluid and urine showed smaller increases in levels of enzyme activity (e. g. 7- and 3-fold respectively for arylsulfatase A). Examination of both the culture and medium and extracellular fluids of I-Cell patients revealed the absence of nonlysosomal enzymes: transaminase, creatinine kinase and lactic acid dehydrogenase. The excessive lysosomal activities in extracellular fluids suggested that there may be a significant cellular leakage in vivo of lysosomal hydrolases and that the observed reduction in the activities of multiple lysosomal hydrolases in cultured cells could be an expression of the primary defect of I-Cell disease.

The studies indicated above suggest that the deficient enzymes (B-galactosidase, alpha-fucosidase and possibly arylsulfatase A) are normally produced in vivo (body fluids) and in vitro (fibroblasts) of I-Cell patients since the activities of these lysosomal hydrolases can be demonstrated in body fluids and in culture medium in which I-Cell fibroblasts are grown.

Since most of the hydrolases are membrane bound, an apparent leakage is indicative of impairment in the membrane structure.

The enzymes leaked are apparently normal, since they react with the same substrates as those isolated by the conventional methods, it is safe to conclude that no co-factor or membrane component is required to alter their enzymatic activities.

Future studies: Prior to elucidating any mechanisms for the pathogenesis of I-Cell disease, a study is needed to characterize several of the affected

enzyme activities. Crude dialyzed preparations of B-D-galactosidase, and alpha-L-fucosidase obtained from various I-Cell disease source will be characterized electrophoretically, kinetically, and thermally (activity profile with increasing temperature). The enzymes excreted by I-Cells are suggested to be more resistant to heating at 50° and more stable to freezing than the corresponding normal controls. Thus far, a detailed study has not been carried out involving the above properties of either the reduced enzyme activities in I-Cell cultured fibroblasts and tissues, or the enhanced enzyme activities present in I-Cell conditioned medium. The properties of these hydrolases, determined by the above experiments, may indicate that there are structural differences between these enzymes in the disease and normal states.

GM2 - gangliosidosis
Tay-Sachs disease, Sandhoff's disease and
Juvenile GM2 gangliosidosis

It is currently believed that the neuronal cytoplasmic storage which occurs in the GM2 gangliosidosis is GM2 ganglioside, and the defective enzyme which is unable to degrade this compound has been identified. There is a generalized absence of hexosaminidase A in Tay-Sachs disease and near absence of hexosaminidases A and B in juvenile GM2 gangliosidosis. In the above mentioned studies it was demonstrated that: (a) the enzymic defect persists in cultured fibroblasts over many cellular generations, (b) soluble endogenous inhibitors did not account for the enzymic deficiency, (c) heterozygotes had intermediate reductions of activity, (d) the defect was present in all tissues studied, (e) prenatal diagnosis of each disorder was possible by enzyme assay of amniotic cells obtained by amniocentesis, (f) both hexosaminidase A and B catalyze the hydrolysis of the terminal N-acetylgalactosamine residue of asialo-GM2 and globoside, while only hexosaminidase A catalyzes the hydrolysis of the N-acetylgalactosamine from GM2.

The mutation in each of the ganglioside storage disease is inherited in an autosomal recessive manner. Cultured fibroblasts from heterozygotes exhibit an enzymatic activity which is approximately 50% of normal levels. These results strongly suggest a strict gene-dosage effect for the expression of the mutant gene leading to the synthesis of a mutant protein with deficient enzyme activity. The existence of a structural gene mutation must be proven by studies involving both normal and disease tissue. In the GM2 gangliosidoses several laboratories have used either highly purified or homogeneous hexosaminidase A and or B to obtain antisera to each protein. These studies have demonstrated that (1) hexosaminidase A and B cross-react immunologically, (2) cross-reacting material against hexosaminidase A and B is present in tissues from patients with Sandhoff's disease, and (3) cross-reacting material against hexosaminidase A is not detected in tissue samples from Tay-Sachs disease.

Hexosaminidases: In spite of an explosion of knowledge about the ganglioside storage diseases in the recent years, the precise mechanism whereby the genetic mutation leads to deficient enzyme activity in each disease is not yet known. The following hypotheses have been postulated to account for the GM2 gangliosidoses.

Hypothesis 1: Hexosaminidase B is normally converted to hexosaminidase A by asialyltransferase, and the defect in Tay-Sachs disease is the absence or alteration of the enzyme, transferase. Thus, hexosaminidase A would not be present. In Sandhoff's disease, the mutation would result in synthesis of inactive hexosaminidase B. Since the transferase would be active in Sandhoff's disease, hexosaminidase A would be synthesized but inactive. However, using this model, it is extremely difficult to explain how hexosaminidase A activities in heterozygotes are maintained at one-half normal levels, unless both the concentrations of hexosaminidase B and the activity of the transferase were rate-limiting.

Hypothesis 2: Both hexosaminidase A and hexosaminidase B possess common and unique polypeptide chains, e.g. hexosaminidase A: aa, cc and hexosaminidase B: bb, cc. The defect in Tay-Sachs disease is a mutation in the "a" polypeptide, whereas the defect in Sandhoff's disease is in the "c" polypeptide. This model predicts that cross-reacting materials are present in Tay-Sachs tissues which correspond to mutant hexosaminidase A and cross-reacting materials are present in Sandhoff's tissues which correspond to mutant hexosaminidase A and B. This model also suggests that the "a" portion of hexosaminidase A is needed for ganglioside GM2-B-galactosaminide activity and that the replacement of this "portion" in Tay-Sachs disease may be sufficient to reverse the defect, since the "c" "portion" abounds.

Metabolites accumulated: As stated above, hexosaminidase A is deficient in the classical form of Tay-Sachs disease. This conclusion was based on the measurement of B-N-acetylhexosaminidase activity with artificial substrates such as p-nitrophenyl B-N-acetylglucosamine or 4-methylumbelliferyl B-N-acetylglucosamine. In spite of this, there is still no direct proof that hexosaminidase A is the actual enzyme which catabolizes the Tay-Sachs ganglioside GM2. There are apparently several variant forms of GM2 gangliosidosis. The biochemical characteristics of patients with classical Tay-Sachs disease are the large accumulation of GM2 ganglioside in nervous tissue, a many-fold increase of GM2 in extraneural organs and little or no increase of asialo GM2 and globoside in visceral organs. Total hexosaminidase activity is increased in serum and tissues, but hexosaminidase A activity is lacking.

Patients with Sandhoff's disease with clinical record of classical Tay-Sachs disease show a transient enlargement of the spleen and liver. In these patients the GM2 content of the brain was essentially the same as in the classical cases of Tay-Sachs disease, but with an extensive storage of asialo GM2 and globoside in neural and visceral organs. The brain and other organs of these patients were completely devoid of both hexosaminidase A and B activities. In view of the complete absence of hexosaminidases of this variant form of Tay-Sachs disease, mucopolysaccharides and glycoproteins might be expected to accumulate; however no such finding was reported.

The Tay-Sachs disease (juvenile form) is characterized by the accumulation of GM2 ganglioside with slight increase of both hexosaminidase A and B activity in brain tissue. The storage of GM2 ganglioside in the juvenile variant is particularly hard to explain. The accumulation of GM2 ganglioside cannot be explained simply as the result of an enzyme defect, since both hexosaminidase A and B are normal or even enhanced in the brain.

Mechanism of enzymatic reaction: The role of B-N acetylhexosaminidase in the degradation of the B-N acetylgalactosaminy residue in GM2 ganglioside and in other hexosamine-containing complex carbohydrate chains has not been elucidated. It has been found that the terminal B-N acetylgalactosaminy residue in the intact Tay-Sachs ganglioside is resistant to B-N acetylhexosaminidase isolated from normal human brain, liver, kidney and urine. It was found that none of the B-N acetylhexosaminidase preparations were able to cleave the terminal N-acetylgalactosaminy residue from the intact ganglioside. Although hexosaminidases seem to be the key enzymes which can unlock the etiology of GM2 gangliosidosis and related diseases, very little is known about the nature of the various hexosaminidase isoenzymes in different tissues.

Although the etiology of sphingolipid storage disease has been shown to be the congenital defect of a specific glycosidase, the precise role of the glycosidase in the disease process remains to be established. For example, classical Tay-Sachs disease is known to be due to the lack of hexosaminidase A. Yet enzyme B is not lacking in this disease and enzymes A and B are equally active in vitro. (A and B enzymes are two isoenzymes for hexosaminidase. Enzyme A has an isoelectric point around pH 5 and enzyme B around pH 7.) Why enzyme B is not functional in vivo remains to be explained. Furthermore, hexosaminidase isolated from human tissue or other sources hydrolyzes terminal B-N-acetylgalactosaminy unit in Tay-Sachs ganglioside, GM2, with great difficulty. It is apparent, therefore, that the biochemical basis of this disease as well as other lipid storage diseases is not as simple as had been thought. More studies are needed to elucidate the actual relationship between the glycosidases and disease. The fact that hexosaminidase is not able to cleave the intact Tay-Sachs ganglioside, but is capable of hydrolyzing its asialo derivative, suggests that the N-acetylneuraminic acid residue hinders the GalNAcGal linkage thus the NANGal linkage is indeed sterically hindered. The possibility of the sialic acid residue to form an inner ester may also be considered. Little attention has been paid to this aspect in the past. Further research will provide an unusual opportunity for a careful examination of the glycan specificity of the various glycosidases as well as the effect of the aglycan moiety on the specificity of glycosidases.

GM1 Gangliosidosis and Globoid Leukodystrophy
Generalized gangliosidosis (GM1 gangliosidosis Type I and II)
Krabbe's disease (globoid leukodystrophy; GLD)

There are three distinct lipid storage diseases in which a deficiency of beta-galactosidase has been determined to be the primary defect. In generalized gangliosidosis (GM1 Type I) the lipid accumulated is GM1 ganglioside and in juvenile gangliosidosis (GM1 Type II) in place of GM1, its asialo derivative is stored in brain and viscera. Globoid leukodystrophy (GLD) on the other hand is a disease which does not involve gangliosides; its suspected lipid metabolite is cerebroside (galactocerebroside and/or psychosine?). Since in all these three diseases the enzyme which is either deficient or inoperative is beta-galactosidase, they have been grouped together under the same section.

In addition to these three recognized genetic diseases with B-galactosidase deficiency, variants which have milder or more severe symptoms are constantly being identified. These are collectively called mucopolysaccharidoses, and include Hurler's, Hunter's and Sanfilippo syndromes. In addition to decrease in B-galactosidase noted in the tissue from patients with mucopolysaccharidoses, decrease in the activity of two isozymic forms of B-galactosidase was also observed when the activities were measured with synthetic substrates. The evidence for the primary defect of B-galactosidase activity in these three mucopolysaccharidoses is slim and probably reflects some as yet unknown compensatory mechanism on the part of the diseased tissue. Indeed, if it were the primary lesion in these disorders, it should be manifest in fibroblasts grown in tissue culture. It is interesting, however, that only B-galactosidase activity appears to decrease in certain tissues in these genetic diseases, while the activities of other lysosomal enzymes are normal or increased.

Distinguishing features of three types of diseases involving beta-galactosidase: Of the main three lipid storage diseases, a deficiency of B-galactosidase activity has been demonstrated with natural and synthetic substrates for GM1 Type I and Type II and only using natural glycolipids substrate in Krabbe's disease. One of the unique distinguishing features in Krabbe's disorder is the lack of overt accumulation of galactocerebroside, despite the catabolic block in the terminal degradative enzyme, B-galactosidase. On the other hand, in addition to genetic block in B-galactosidase, children with generalized gangliosidosis do accumulate GM1 ganglioside, whereas in Juvenile gangliosidosis, in addition to GM1, its asialo derivative is also accumulated in brain and viscera. It is interesting to note that even though GM1 ganglioside is accumulated in the brain, enzyme preparations from cerebral gray matter of these subjects (Type I & II) showed normal or above normal activity of B-galactosidase when reacted with galacto-, lact-, and glucoceramide, whereas preparations from livers of these patients demonstrated virtual absence of B-galactosidase. In practice the activity of this enzyme is normally visualized using a fluorescent substrate, 4-methyl umbelliferyl-B-galactosidase. Therefore, it appears that GM1 ganglioside-B-galactosidase activity is mimicked by these synthetic substrates, (4 MU-B-gal and p-NP-B-gal). The use of these two synthetic substrates has been made a routine assay in the diagnosis of Type I and II ganglioside storage diseases in many laboratories when a suitable enzyme source is to be tested.

Krabbe's disease can be differentiated from Type I & II GM1 gangliosidosis by using natural and synthetic substrates: The main characteristic of Krabbe's disease is deficiency of B-galactosidase activity towards its natural substrate, galactosyl-ceramide. Further work indicated that these patients were also deficient in catabolic activity towards psychosine (acylated galactose-ceramide), monogalactosyl-diglyceride and lactosyl-ceramide.

On the other hand, using synthetic substrates, 4-MU-B-galactose and P-nitrophenyl B-galactose, the enzyme preparation from Krabbe's patients showed no defect in B-galactosidase activity.

In general, it may be concluded that Krabbe's disease can be demonstrated by inactivity of enzyme preparation towards its natural substrates and by positive action when reacted with synthetic substrates. In contrast, in Type I and II diseases, B-galactosidase is active in gray matter and can be shown when reacted with both synthetic and natural substrates.

Pathogenesis of Globoid Cell Leukodystrophy (GLD): A series of studies has largely clarified the underlying genetic cause of both human and canine globoid cell leukodystrophy (GLD), Krabbe's disease and has contributed to better understanding of its pathophysiology. However, there are still some unanswered questions regarding the precise pathogenetic mechanism of the disease. As stated above, one of the unique characteristics of GLD is the lack of overt accumulation of galactocerebroside, despite the metabolic block in its immediate terminal degradative step. Except for the unlikely possibility that excess galactocerebroside can be removed from the brain, the only possible explanation would be the cessation of galactocerebroside synthesis by whatever the mechanism. It has been suggested that the almost complete loss of oligodendroglia in the brain of patients might explain the termination of galactocerebroside biosynthesis. However, later finding of the absence of specific galactocerebroside accumulation in the normal kidney suggested another possibility that there might be a metabolic regulatory mechanism which shuts off galactocerebroside biosynthesis in the presence of the degradative block. Furthermore, the finding of the simultaneous deficiency of psychosine degradation provided the possibility of this cytotoxic compound to be responsible for the devastating oligodendroglial cell loss.

Possible Role of Psychosine in the Pathogenesis of GLD: As stated above a unique feature of the GLD is the lack of overt accumulation of galactosylceramide in the brain despite the block in its degradation. This appears to result from the very rapid disappearance of oligodendroglial cells during the course of the disease. In order to explain this unique biochemical pathogenesis of GLD, a hypothesis was proposed, now referred to as the psychosine hypothesis. This was based on the findings that psychosine (galactosylsphingosine) is also a substrate of galactosylceramidase and that it is highly cytotoxic. The hypothesis postulates that galactosylsphingosine, rather than galactosylceramide, might be the compound responsible for the unusually rapid demise of the oligodendroglia. The results so far have been consistent with this hypothesis. Furthermore, it received strong support when recently for the first time, the amount of psychosine in GLD brains was found to be 10-100 times that of normal brain. Even at this concentration, the absolute amount is extremely small. Nonetheless, there appears some credibility to the role of psychosine in the pathogenesis of GLD.

Animal models for GM1 gangliosidosis: Recently, a feline model of GM1 gangliosidosis has become available. The following analogous characteristics with human GM1 gangliosidosis Type II have been established: Feline GM1 gangliosidosis is an autosomal recessive trait involving altered catabolism of GM1 ganglioside. The disease in cats is indistinguishable from the human disease biochemically. An in vitro fibroblast culture system has been developed which serves as a basis for in vitro studies of this disorder. Preliminary investigations of renal transplantation and parabiosis failed to

support the thesis that renal transplantation offers promise as a method for providing active enzyme to mutant cats. A highly purified GM1 ganglioside B-galactosidase has been isolated from normal cat brain and liver, and used for biochemical characterization of this lysosomal hydrolase including comparisons with mutant (immunologically cross-reactive) enzyme. Purified enzyme has also been used in preliminary studies of the fate, distribution and metabolic effect of exogenous enzyme administration to mutant cats.

Further investigations are being conducted to: Elucidate the factors which influence uptake and metabolic utilization of exogenous enzyme by mutant tissues, develop "packaging" techniques or molecular modification of exogenous enzyme to facilitate stability, uptake and hydrolytic function. Investigate lysosomal hydrolase administration techniques which may overcome treatment limitations imposed by the blood-brain barrier, define any deleterious physiological consequences of repeated administration of purified exogenous lysosomal hydrolases, and to evaluate the ability of cells to recover from prolonged dysfunction, following correction of the metabolic defect by enzyme therapy.

A canine model of human Krabbe's disease is also available, in which B-galactosidase deficiency has been confirmed, including detection of an intermediate, heterozygous activity level in the histopathologically normal brain. Three genotypic levels of B-galactosidase activities are found in human serum, leukocytes and fibroblasts. These three activity levels have been confirmed in dogs, but in canine serum from normal heterozygous and affected, all had similar activity levels. With the exception of this difference in serum activity, all other catabolic deficiencies in nervous tissue and other pathological processes are virtually identical to human Krabbe's disease.

Utilizing dogs as animal models of human disease, the following aspects of this disease are being investigated: Determination of morphological features which enable certain white matter regions to resist lesion formation compared to susceptible regions, and determination of the nature and extent of the enzymatic deficiencies responsible for white matter degeneration observed in Krabbe's disease.

Heredopathia Atactica Polyneuritiformis
(Phytanic Acid Storage Disease Refsum's Disease)

In 1946, a new inherited neurological syndrome was identified called Heredopathia Atactica Polyneuritiformis. It is also called phytanic acid disease or Refsum's disease named after its discoverer. It was shown that patients with this syndrome accumulated in tissues and serum an unusual branched-chain 20-carbon fatty acid, phytanic acid (3,7,11,15-tetramethylhexadecanoic acid). Clinical studies established that there was little or no endogenous biosynthesis of phytanic acid; phytol and phytanic acid were identified as dietary constituents. The normal pathway for phytanic acid degradation was shown to involve an initial alpha-oxidative attack, leading to the formation of alpha-hydroxyphytanic acid, followed by decarboxylation to yield the (n-1) fatty acid pristanic acid, and finally a series of successive beta-oxidations to CO₂.

Pathogenesis: The pathogenesis of the neurological syndrome remains uncertain but there is reason to believe that phytanic acid accumulation, directly or indirectly is responsible. The possibility was considered that accumulation

of phytanate might be a reflection of a more general defect (e.g. a general defect in fatty acid alpha-hydroxylation) and that the neural changes related not necessarily to phytanate accumulation per se. However, analyses of skin lipids from patients with Refsum's disease showed normal concentrations of straight-chain alpha-hydroxy fatty acids. Furthermore, several important differences between the straight-chain alpha-hydroxylation system of brain and the alpha-hydroxylation system for phytanic acid catabolism have been described. For example, the brain system is microsomal whereas the phytanic acid oxidation system is mitochondrial; attempts to demonstrate phytanate oxidation in brain have been negative; the brain system for straight-chain oxidation is stimulated by ferrous ion while the phytanic acid oxidation system in liver is inhibited. Because of the close structural relationship between the side chain of vitamin E and the structure of phytanic acid, the possibility that pathogenesis is related to a defect in vitamin E function or metabolism had to be considered. However, direct study failed to reveal any defect in vitamin E metabolism or in vitamin E levels. The best evidence that the pathogenesis relates to phytanate accumulation comes from the improvement seen clinically when phytanate levels are reduced in diet.

Pathogenetic role of Phytanic Acid: Accumulation of phytanic acid in hereditary ataxia polyneuritiformis not only means that the clinical signs are a direct result of such a product, it also indicates evidence of a metabolic block. The fact that although liver, heart, peripheral nerves, CSF, and even parts of the retina contain an excess of phytanic acid, the brain contains only small amounts, and the so-called blood-brain barrier must be relatively impermeable to phytanic acid. It has been shown that changes are present in liver, heart, and kidney not only with regard to phytanic acid content, but also in levels of cholesterol. Death of patients may well be associated with the cholesterol accumulation rather than with an increase in an unusual fatty acid.

High levels of phytanic acid (serum phytanic values above 100 mg/100 ml) may cause acute toxic symptoms in patients as well as in experimental animals. The subject loses weight and fails to thrive. Increasing fatigue and death appear to occur at serum levels ranging between 200 to 250 mg/100 ml.

Animal studies: Several loading experiments with phytanic acid have been carried out in animals in order to provoke symptoms and signs resembling Refsum's disease. Large amounts of phytanic acid caused toxic effects, but did not produce any clinical signs or histological manifestations resembling hereditary ataxia polyneuritiformis in the nervous system. However, analysis of the brain lipids showed incorporation of only trace amounts of phytanic acid, in contrast to what has been found in nervous tissue from patients. It seems clear that phytanic acid accumulates much more easily in the nervous tissue of patients than in brain and nerves of experimental animals on long-term phytanic acid feeding. The mechanism behind the different degree of incorporation is unknown. However, it is reasonable to assume that this difference explains why it has been impossible to mimic the nervous system symptoms in animals. Hence, these experiments do not speak against a causal relationship between the accumulation of phytanic acid and the nervous lesions.

Genetics: The overall rarity of phytanic acid storage disease together with its occurrence in more than one child in a sibship strongly indicated a Mendelian recessive inheritance pattern and the almost equal occurrence in males and females indicated an autosomal character. Further studies established the existence of a biochemically identifiable carrier state. Fibroblast cultures derived from unaffected siblings or from parents of patients with phytanic acid storage disease were shown to oxidize added phytanic acid at a rate approximately 50% of that seen in control fibroblast cultures. There was little or no overlap between the results in presumed heterozygotes and those in controls. The availability of a method for identifying the carrier state may prove helpful in certain clinical situations. For example, siblings of clinical cases can be studied to ascertain whether they do or do not have the defect early in life. Since intervention with appropriate diet appears to arrest progression, identification of cases as early as possible has potentially important implications. With the development of safe techniques for amniocentesis it is now possible to identify either the homozygous or the heterozygous state in utero.

Nature of Enzyme defect: As stated earlier, the normal pathway for phytanic acid degradation follows an unusual initial alpha-oxidative attack, leading to the formation of alpha-hydroxyphytanic acid, followed by decarboxylation to yield the (n-1) fatty acid, pristanic acid which is further degraded by a series of successive beta-oxidations resulting in acids such as acetic, butyric, dimethylacetic, etc., and finally to CO₂. It has been shown that patients with phytanic acid storage disease and skin fibroblast cultures derived from them showed a marked reduced rate of conversion of phytanic acid to CO₂. It was also shown that the rate of oxidation of pristanic acid, the second identified intermediate in the degradative pathway, was quite normal both in vivo and in cell culture. Further investigation indicated that the enzymatic error lies specifically in the production of alpha-hydroxyphytanic acid. This follows from the fact that the rates of oxidation of pristanic acid and of alpha-hydroxyphytanic acid are normal in patients who show a marked defect in the rate of oxidation of phytanic acid itself. Further support comes from the fact that fibroblasts in culture likewise oxidize pristanic acid and alpha-hydroxyphytanic acid normally while showing a severe defect in phytanic acid oxidation. Disassociation between the oxidation of phytanic acid and of its hydroxyl derivative has now been demonstrated in 8 different cell lines representing 8 different kinships. Thus, there is no evidence for a clinical syndrome with phytanic acid storage other than on the basis of a defect in alpha-hydroxylation since the straight-chain alpha-hydroxy acid levels in patients appear to be normal.

Over the past several years something like 100 serum samples from all over the United States and from abroad have been analyzed because of a clinical suspicion of Refsum's syndrome. Only three new examples of phytanic acid storage disease have been encountered -- one sibship in England, one in France and one here in the United States. Combined with the extensive screening that has been done at other centers (especially in Oslo and the previous screening done at the National Institutes of Health), these findings justify the conclusion that this is in fact a rare mutation and that its infrequent occurrence does not simply reflect a low index of clinical suspicion. Certainly, at all

major neurologic centers the possibility of phytanic acid storage disease appears in the differential diagnosis of every patient with unexplained peripheral neuropathy and/or unexplained retinitis pigmentosa.

Treatment: Soon after it was established that phytanic acid was not endogenously synthesized but had its origin in the diet, it was possible to show a decrease in serum phytanic acid levels in patients placed on diets containing low levels of phytol and phytanic acid (fat and chlorophyll free diet). Two patients were studied on this special diet. These studies showed, in addition to the expected fall in plasma phytanic acid levels, improvement in nerve conduction velocity, improvement in some tests of muscle strength, restoration of peripheral sense modalities in some areas, reversion of EEG to a normal pattern and subjective clinical improvement.

As an emergency measure, patients with very high levels of phytanic acid may be treated by plasmapheresis. Once a week over a period of several months, 400 ml of plasma was removed, the blood corpuscles being reinjected into the patients. This technique was found to be an excellent adjuvant to the dietary treatment with a low-phytol low-phytanic acid diet. Excellent correlation between the reduction in serum phytanic levels and the clinical improvement in muscular strength and ataxia was seen.

Future studies: Assuming that accumulation of phytanate itself initiates the changes that lead to nerve dysfunction, it is proposed to explore the effects of incorporation of phytanate on cell function and structure. The possibilities that are considered include: 1) that incorporation of phytanate into myelin alters its structure such that it is unstable and undergoes dissolution more rapidly than it can be repaired: 2) that incorporation of phytanate into glial cells (or Schwann cells) relates to pathogenesis by interfering with repair processes or by inducing release of lytic enzymes: 3) that incorporation of phytanate into certain specific lipid components rather than overall phytanate incorporation is relevant to pathogenesis e.g., phospholipids or complex lipids in critical sites in membranes may be altered by incorporation of phytanate so that the membrane or subcellular particle is altered functionally.

Batten Disease (Neuronal Ceroid-lipofuscinosis NCL)

Batten disease (late infantile and juvenile lipidosis) and other disorders of lipofuscin accumulation cause long term, progressive mental disability and blindness in infants and children, and sometimes in adults (Kufs disease). By a series of histochemical and chemical studies the NCL has been defined as a group of heritable degenerative diseases with maximum effect on the brain. These diseases were considered as familial amaurotic idiocies resulting from lysosomal accumulation of gangliosides. To the contrary, it is now believed that the neuronal ceroid-lipofuscinoses are due to the accumulation of autofluorescent lipopigments resulting from an enhanced rate of peroxidation of polyunsaturated fatty acids. The hypothesis was advanced that the degradation of tissue peroxides is deficient, an assumption seemingly supported by the observation of markedly reduced activity of a p-phenylene diamine

(PPD)-mediated peroxidase. However, certain conceptual difficulties have arisen because the enzyme is deficient in at least three different human types of neuronal ceroid-lipofuscinosis, the acute Jansky-Bielschowsky and the chronic Spielmeier-Sjogren type, both inherited as autosomal recessives, and also in the adult form, which is inherited as an autosomal dominant. Furthermore, the same enzyme is deficient in English Setters with neuronal ceroid-lipofuscinosis. In other words, an identical enzyme defect which satisfactorily explains the pathogenesis is encountered in presumably different genetic defects producing different clinical but similar pathomorphologic phenotypes.

Genetics: The disease follows strictly Mendelian recessive inheritance characteristics. This statement is verified by the fact that the activities of heterozygotes have shown PPD-peroxidase activities values in between those of normal controls and of homozygous affected. The same Mendelian ratio has been observed in experimental animals, English Setters.

Substrate for PPD-Peroxidase: A difficulty arises from the fact that the physiological substrate for the PPD-mediated peroxidase is unknown. The procedure which reveals the activity of this peroxidase with substrate p-phenylenediamine is only 20% and 5% as efficient as a hydrogen donor as are methoxybenzidine and guaiacol respectively. Nevertheless, with these two substrates the enzyme defect cannot be demonstrated and it appears that the physiological substrate for the PPD-mediated peroxidase represents a group of heterogeneous proteins, as for example, catalase.

Leukocytes: It has been observed that the PPD-peroxidase deficiency can be demonstrated only when leukocytic extract is prepared in a special manner; i.e., after freezing and thawing of white cells. Only with the soluble fraction of peripheral white cells can the deficiency of PPD-mediated peroxidase be demonstrated when compared to the similar preparation from normal individuals. There is no deficiency of this enzyme in these patients when whole leukocytes or the soluble and membrane components are combined. There is no satisfactory explanation for the deficiency of PPD-peroxidase in a soluble fraction. Using this soluble preparation with p-phenylenediamine, O-dianisidine and guaiacol as hydrogen donors, the leukocytes of NCL patients were found to be deficient in peroxidase activity. Using another agent, nitro-blue tetrazolium (NBT), reduction values in the leukocytes of the patient were also found to be significantly higher than normal controls, indicating the impairment in the hydrogen peroxide catabolism. The determination of NBT and leukocyte peroxidase may also serve as a diagnostic test for NCL disease.

Prenatal diagnosis of NCL: A simple assay of peroxidase in amniotic fluid is being developed. A narrow range of activity was defined between 17 weeks and term in normal human pregnancies. From 30 weeks to term, normal enzyme activity increased forty-fold. This increase is due primarily to the maturation of the fetal salivary gland. Though the opportunity to test this procedure has not yet arisen in humans, it may prove useful in future studies where a human fetus is at risk. Presently, experiments are planned to measure amniotic fluid peroxidase in the dog model.

Metabolites accumulated: The hypothesis is that the pathomorphologic and clinical manifestations of the neuronal ceroid-lipofuscinoses (NCL), namely the canonically conjugated formation of autofluorescent lipopigments and progressive nerve cell death are the result of an increased rate of peroxidation of unsaturated fatty acids. The lipopigments isolated from NCL patients consist of more than 50% of an acidic fatty acid polymer. On the other hand, there is no accumulation of any one glycolipid or phospholipid. In fact, these complex lipids have concentrations smaller than those obtained from whole brain homogenates. The same applies to neutral lipids and fatty acids. Only one lipid is consistently increased in these pigments, namely lysobisphosphatidic acid, the nature of this increase remains unknown. Although the elevated concentration of this presumed intermediary is, on the relative basis, quite high, its absolute concentration is so low that it seems highly improbable that lysobisphosphatidic acid would represent the primary non-degradable compound leading to the accumulation of lipopigment.

Although most investigators still believe that ceroid-lipofuscin is accumulated as a result of peroxidation of unsaturated fatty acid, a considerable doubt exists as to the nature and the origin of this autofluorescent pigment. For example, cytosomes filled with intensely fluorescent material in the form of curvilinear bodies were isolated from the cerebral cortex of a child who had died at age 7 from the late infantile form of Batten disease. Forty-three percent of the dry weight of the storage material was analyzed by the most sophisticated modern technology. The results indicated the presence of retinoyl polyenes linked to a small peptide. Upon further hydrolysis and metholysis, this compound yielded retinoic acid and methyl retinoate, respectively. On ozonolysis of these components, a product was obtained which was similar to the one obtained from the substituted cyclohexenyl ring of Vitamin A. The results indicate that the fluorescent component of the neuronal storage material is a retinoyl complex and is not derived from peroxidized polyunsaturated fatty acid as previously thought. Not only is there a controversy regarding the nature of the pigment, a considerable disagreement also exists about the identity of the missing "peroxidase." Also, the assessment of peroxidase activities in various tissues is open to question. The different peroxidases which are known are unique proteins and it does not necessarily follow that if one peroxidase is abnormal, others, for example, myeloperoxidase, lactoperoxidase, thyroid peroxidase and glutathione peroxidase, etc., would also be abnormal. In fact, disorders are known that specifically affect only one of these enzymes without involving the others. PPD-mediated peroxidase is a nonspecific entity with unknown physiological substrates. Complete reliance on this pathological condition as to the basis of these disorders is an unrealistic inference at this time.

Experimental treatment with antioxidants: In order to test the hypothesis that Batten disease may be associated with an increased rate of unsaturated fatty acid peroxidation, dogs, English Setters with this disease were fed controlled diet containing antioxidant drug. These trials revealed that vitamin E in daily doses of 400 mg per day at the age of 7 months or earlier

delayed the onset of this disease by approximately 2-3 months, however, this treatment did not improve the life span. Also, vitamin E given with the onset of symptoms was ineffective. If the treatment is initiated at the earliest age, it is possible to produce 100% homozygous affected offsprings by mating affected animals which had been pretreated with vitamin E.

Treatment of human NCL patients showed that EEG abnormalities are occasionally improved or at least do not deteriorate at the same rate as in untreated patients. Also, the intellectual performance is maintained at a stationary level for years, but visual deterioration is not retarded. It should be pointed out that others who have used this treatment have not been able to confirm these results.

Experimental enzyme therapy: Enzyme therapy in genetic diseases has not produced encouraging results in a number of lysosomal diseases. however it appears that not all possibilities have been fully explored. Experience with kidney exchange transplanation between two litter mates, one affected, the other a heterozygote, has not produced any tangible results.

On the other hand, among four homozygous affected dogs who received various combinations of splenic and bone marrow transplants at the time of birth, one has shown consistently normal peroxidase activity whereas the other three have typical values of affecteds. Since homozygous children at risk can be identified before the onset of the disease, the projected studies may lead to a more direct and curative treatment than the antioxidant regimen, provided that the biochemical studies implicate PPD-peroxidase deficiency as the probable etiology of NCL.

Adreno-Leukodystrophy ALD (X-linked Schilder's Disease)

Schilder's disease is characterized by two clinical abnormalities. One related to adrenal insufficiency and other related to cerebral dysfunction. There is also a possiblity that other abnormalities hitherto unidentified may also be involved. Several cases of adreno-leukodystrophy have been identified, all occurring in males.

The disease is X-chromosome linked (as in Fabry's disease) which means that only mothers are carriers of recessive trait resulting in one-half of male affected children, the other half will be normal.

Symptoms: The neurological symptoms have usually manifested themselves between the ages of 5-15 years. The initial symptoms are often behavioral and academic apathy. Decreasing vision with subsequent development of optic atrophy and loss of pupillary reaction to light. A spastic ataxic gait soon becomes evident with eventual quadriplegia and decorticate posturing. Focal or generalized seizures may occur late in the illness. Peripheral neuropathy and fasciculations have not been observed. Death has been the inevitable outcome, usually between one and five years after the first neurological finding. Electroencephalographic findings have revealed initial delta foci in the posterior hemispheres. The area of the delta activity

increases as the disease progresses. Isotope brain scans have revealed an early increased uptake of isotope in the parieto-occipital lobes in two cases. Elevated cerebrospinal protein is a common finding, sometimes with an increase in gamma globulin. The combination of an abnormal brain scan, elevated CSF protein and EEG slowing has occasionally led to a mistaken diagnosis of brain tumor.

Electron microscopic studies of the adrenal gland and of a small peripheral nerve fascicle present in the adrenal capsule from ALD patients were conducted. In the zona fasciculata, striated cells were present, and the striations proved to be predominantly linear, membrane-like accumulations within the cytoplasm. These accumulations often consisted of rows of paired, electron-dense leaflets each 25A thick, separated by a clear space which varied between 20A and 70A. Similar profiles were found in the cytoplasm of some of the Schwann cells surrounding myelinated axons in the small capsular nerve. The membrane-like appearance suggested these accumulations might be composed of lipoprotein and lipid. The presence of similar changes in the Schwann cells and adrenal cells further support the hypothesis of a related metabolic defect in adrenal and nervous system.

Biochemical studies: There have been three biochemical studies of brain biopsy tissue from ALD and none has identified a specific error in lipid metabolism. Some workers have demonstrated a near-normal lipid content in severely affected areas of white matter while others have shown chemically abnormal myelin with increased cholesterol esters. These findings reflected a non-specific process of myelin destruction. A recent investigation of cholesterol metabolism in fibroblast cultures from patients with ALD, revealed the uptake of cholesterol and cholesterol palmitate to be similar to control fibroblast cultures, however, the ALD cultures accumulated greater amounts of both substances on continuous exposure. These data are stated to be consistent with ALD being a generalized defect in cholesterol metabolism.

Adrenal insufficiency: The pathological changes in the adrenal have received little attention. Adrenal atrophy has usually been described as severe. Some of the patients have not received steroids, hence the adrenal atrophy has not been considered secondary. No significant abnormalities of the pituitary or adrenal medulla have been described, and the zona glomerulosa of the adrenal cortex has been relatively preserved. Changes consisting of a loss of cells without an inflammatory infiltrate have been described in the zona fasciculata and reticularis.

In some patients the clinical history of adrenal cortical insufficiency has been present for as long as seven years prior to the onset of neurological disease. The earliest recorded onset of adrenal insufficiency is at 3 years. Serum electrolyte abnormalities have been rare. Melanoderma, in combination with reduced response to ACTH infusion, has indicated that the adrenal disease has been primary in these patients. Initiation of steroid therapy has not prevented the development of the demyelinating process, nor modified the relentless course once the process has started.

Rationale for future studies: The simultaneous destruction of adrenal cortex, and CNS myelin in a hereditary disease has suggested that ALD is a lipidosis. This notion has been reinforced by the presence of ultrastructurally similar cytoplasmic inclusions in adrenal cortical cells, Schwann cells, testis and brain macrophages. Since adrenal cortex, testis and CNS myelin contain large amounts of cholesterol, a logical beginning for the biochemical studies is the examination of cholesterol metabolism in fibroblast cultures from patients with ALD. Another promising biochemical investigation centers around the isolation of the inclusions and their chemical characterization.

Ultrastructural and light microscopic analysis of the nervous system and endocrine changes will be of great help in understanding the evolution of the disease. The rationale for the intense study of the demyelinating process and the immunological status of these patients stems from the resemblance of the central nervous system changes to those of multiple sclerosis. Both ALD and multiple sclerosis are inflammatory demyelinating conditions and there is evidence that immunologic factors have a role in the demyelinating process of MS. An investigation for a possible immunologic component in ALD may yield results that explain the radically different light microscopic appearance and clinical courses of the CNS and adrenal process.

Cerebro-hepato-renal Syndrome (Zellweger Disease)

Zellweger disease is characterized by the absence of peroxisomes and impaired capacity of mitochondria in electron transport system. This is a rare, fatal and heritable disease. Zellweger disease seems, therefore, the first inheritable cirrhosis apparently due to, or associated with abnormal mitochondrial functions. This conclusion resulted from biochemical and morphologic studies of initial enzyme histochemical staining reactions performed on liver obtained by conventional biopsy techniques.

Despite morphologic absence of peroxisomes, total catalase activity was normal in the one liver examined. Is catalase in Zellweger's syndrome soluble rather than peroxisome-bound? The cytochemical staining procedure which differentiates soluble from peroxisome-bound catalase will be utilized to study this important question. Because the liver of these children is cirrhotic, techniques developed for subcellular fractionation of homogenates of needle biopsies cannot be utilized. Similar enzyme histochemical studies will be performed in the heterozygote parents of the children when possible.

These studies should provide clues regarding the function of peroxisomes and the relationship between absent peroxisomes, normal catalase activity, impaired mitochondrial electron transport and inheritable cirrhosis.

Antenatal diagnosis of Zellweger Disease has been attempted with cytochemical studies of mitochondrial oxidative activities on unfixed cultured cells obtained by amniocentesis. In the initial screening test, cells were incubated for succinoxidase and other mitochondrial oxidative activities with either menadione or phenazine methosulfate, as intermediate

electron acceptor. In the cerebro-hepato-renal syndrome, mitochondria have severely reduced capacity to oxidize succinate with menadione. In two instances, staining reactions were normal; normal children were born. Whether the mitochondrial abnormality in this syndrome can be utilized in antenatal diagnosis is, therefore, not yet known. Additional cultures will be utilized to test this possibility.

Lafora form of Myoclonic Epilepsy

This fatal disorder afflicts adolescents and young adults. Characteristic, nonlysosomal, mucopolysaccharide inclusions are present in the brain, and in skeletal muscle, which are considered to be altered peroxisomes. Hepatocytes are swollen with PAS-positive material and other organelles are restricted to the periphery of the nucleus. This appearance is described as diagnostic test for Lafora's disease.

Metabolite accumulated: Electron microscopic studies showed that the fibrillar ultrastructure of Lafora bodies is hydrolyzed both by alpha amylase and by gamma amylase. These findings established the fibrillar structures, (rather than the matrix itself), as the polyglucosans. Amorphous densities also disappeared following these amylolytic enzymes, suggesting that they too, were polyglucosan in nature.

Muscle fibers: Highly distinctive light and electron microscopic changes were found in muscle fibers in Lafora disease. For example, an abnormal, prominent stippling pattern occurred in muscle fibers with the NADH-tetrazolium reductase stain. The stippling corresponded to small membrane-bound packets of densely osmiophilic granules. Both larger and smaller granules were entirely removed after one hour of alpha-amylase digestion. Approximately 5% of packets had collections of fibrils strongly resembling those found in the cerebral Lafora bodies. The unique morphological findings in muscle permit one to diagnose this disease of the central nervous system without having to resort to biopsy of the brain. The histochemical reactions of areas of polyglucosan storage in muscle show a strong reaction with diaminobenzidine peroxidase at pH 9, an activity inhibited by 6-aminotriazole, suggesting that catalase was giving this reaction. These observations suggested that in muscle, a peroxisome-like organelle accumulates as the storage material. A clear relationship between peroxisomes and Lafora bodies in the central nervous system remains to be established.

Skin changes: Diagnostically skin changes were found in one patient, in whom the diagnosis was histologically proven. Skin lesions were restricted to the medial surface of the ear lobule, where a number of pores were filled by small blebs.

Serum studies: Serum studies on three patients during life showed they had an absolute decrease in alpha-2 globulins, and an absolute increase in gamma globulins. In contrast, parent and other normal controls did not show these changes.

Urine analysis: Urine studies have shown two sets of changes. In one study, in which Lafora's disease was histologically proven, three affected family members showed an increase in one or two fractions. These were consistent with true glycosaminoglycans (acid mucopolysaccharides) of low sulfate content.

PAIN

The term "Pain" is used in a variety of situations. It is sometimes applied in a physical sense and sometimes to the effect produced by mental processes. Physical events resulting in the perception of pain can be described as those situations in which the body or any part of it comes in contact with objects which under normal conditions are innocuous, but under changed conditions become painful, hurtful, unpleasant, or even unbearable. For example, a bullet placed in the palm of your hand is harmless. The same bullet at an accelerated velocity can produce not only pain, it may even be fatal. Similarly, other altered physical states of objects can produce unpleasant sensation, e.g., acceleration in heat, electricity, wind velocity, etc.

Pain can also be caused by metabolic disturbances, either inherent, induced, or by environmental factors. Psychological processes have a considerable influence in eliciting or suppressing pain. However, these influences are rather hard to assess in strictly scientific terms. Pain is a problem of major importance for two general reasons: in its chronic form it is a clinical problem which touches nearly every aspect of life. As a neurobiological problem, it is important to understand not only what actually pain is, but to know what causes pain, how it is perceived, how the stimulus causing pain is transmitted and where, if any, are pain receptor centers located. Closely related are problems where apparently physical stimulus may cause pain but the underlying biochemical mechanism may be affected so as to either accentuate or even retard the threshold of pain perception. The investigation of pain mechanisms goes well beyond adding essential details to our knowledge of sensory processing and somesthesia. It leads into the studies of molecular mechanisms of receptor activation, somatic, autonomic and neuroendocrine reflex organization; the neural basis of motivation, affect and accompanying emotional states; the neural events providing a necessary condition for learning and the determinants of attentional control over sensory and motor processes.

Current Knowledge of the Neural Mechanism of Pain

Peripheral nerves: Clinical and experimental observations have provided strong evidence that receptors which generate impulses in certain small-diameter myelinated (A-delta) and unmyelinated (C) fibers mediate normal pain sensation. Noxious stimuli which threaten to damage tissue are required to activate these nociceptors. There is evidence that some nociceptors are activated by a substance released from the stimulated tissue. The biochemical and biophysical processes by which this is accomplished are currently under active investigation.

First central synapse: Impulses from nociceptive afferents activate physiologically and anatomically distinct cells in the dorsal gray matter of the spinal cord (dorsal horn) and in the trigeminal sensory nucleus of the brainstem. The former mediates sensation from the body and visceral organs while the latter mediates facial and oral sensations. In both structures, some central neurons appear to respond exclusively to noxious stimuli while others respond to a wider range of stimuli, showing maximal responses to noxious events. The different roles played by these different types of

neurons and the chemical substances mediating their synaptic activation are not yet established.

Pathways for pain in the CNS: A number of central structures and pathways are activated by the impulses ascending from the nociceptive spinal cord and trigeminal nucleus neurons. Some impulses travel a direct route via axons projecting to sets of somesthetic integrative thalamic neurons located between the brainstem and the cerebral cortex. At least 3 separate groups of thalamic neurons receive these direct spinothalamic or trigemino-thalamic projections. Other spinal and trigeminal nociceptive impulses travel one or more indirect routes as they ascend to the brain. These impulses activate neurons within the deep central gray matter (reticular formation) of the spinal cord and brain stem; these reticular formation neurons in turn send ascending projections to the thalamus and hypothalamus and some send descending projections back to spinal cord and brainstem sensory and motor neurons. The functional roles of the direct and indirect pathways are not yet established, but the evidence at hand suggests that the direct spinothalamic and trigeminothalamic pathways are important for discriminating spatial, temporal and intensive features of noxious stimuli while the indirect pathways subserve motivational, autonomic, and other non-discriminative aspects of the pain experience. The role of the cerebral cortex in pain is not known.

Intrinsic mechanisms for pain modulation: At each point of synaptic activation along the pain pathways, the ascending flow of impulses is subject to modulation by the activity of other neurons. The activation of spinal dorsal horn and trigeminal nucleus neurons by nociceptive afferents is modified by concurrent activity in other peripheral afferent fibers. Similarly, fibers descending from certain neurons of the brainstem reticular formation and cerebral cortex can suppress the activation of central cells by noxious stimuli; in some instances, this suppression can be related to behaviorally manifest analgesia. There is evidence that at least some of these intrinsic pain control systems may mediate the analgesic effects of opiates and provide the neural substrate for the analgesic effects of the endogenous morphine-like peptides recently found in the brain. These exciting discoveries have significance well beyond the area of pain research and, among many other possibilities, they provide the opportunity to study pain mechanisms by producing controlled analgesia by a variety of methods.

Significant advances in our understanding of pain mechanisms have been made in recent years. The new knowledge acquired has often contributed to other areas of neuroscience and has provided a new basis for the consideration of new therapeutic approaches. There is little doubt that, with the proper resources, future research will supply the new knowledge which is necessary for continued progress in basic and clinical neuroscience.

Specific Clinical Pain Problems

The specific clinical problems are those in which pain, either chronic or frequently recurring acute pain, is the dominant complaint. Some of the examples are as follows:

Headache and other cranio-facial pain: At least 40 million U.S. citizens are estimated to suffer from chronic recurring headaches of various types throughout a significant fraction of their adult working lives. The mechanism by which pain is produced in the major types of headache is not known. The pain-sensitive structures include muscle, the dura, and dural blood vessels, but little is known of the physical and chemical conditions required for the activation of the nociceptors in these structures. In two other major types of cranio-facial pain, paroxysmal trigeminal neuralgia (tic douloureux) and temporomandibular joint pain-dysfunction syndrome, the mechanisms are no clearer. As a result of lack of understanding of the pathophysiology of these conditions, therapy is often inconsistent and inadequate for many patients; this leads to trials of numerous drugs and ultimately to surgical procedures which may compound the problem by providing another source for pain as a result of postoperative complications.

Low back pain: The causes of this condition are legion, ranging from benign (though disabling) muscle strain and spasm to cancer involving the vertebrae and surrounding tissue. Most low back pain, like headache, is not fatal, but it affects an estimated 14 to 15 million individuals in the United States and is responsible for an estimated 4 to 5 billion dollars in direct medical costs of various kinds. An estimated 93 million work days may be lost each year because of low back pain. A lack of understanding of the pathophysiology of this disorder depends upon our present ignorance of the interactions of the biomechanics of the spine and the supporting pain-sensitive tissues.

Pain due to cancer: Many people fear the pain of cancer more than death. An estimated 345,000 people in the United States die of cancer each year; of these, the majority require relatively prolonged management of chronic or recurring pain. Potent narcotic analgesics are effective and available, but when the disease is protracted, the development of tolerance may be a problem. Ablative neurosurgical operations on the brain or spinal cord are certainly not without risk of mortality or morbidity; many afford effective but only temporary relief and some are associated with an undesired change in the patient's personality. Further refinement of these procedures or continued development of methods for focal electrical stimulation in the brain may lead to more physiologic and specific means of long term pain control.

Pain of other causes: Chronic arthritic pain affects an estimated 20 million people in the United States, but there is little or no information on the number of individuals suffering chronic or recurrent pain from innumerable other disorders such as trigeminal neuralgia, painful neuropathies from nerve injury or diabetes, phantom limb pain, pain due to CNS disease (central pain), or chronic, intractable pain of undetermined etiology. The heterogeneity of this group emphasizes the diversity of conditions in which pain is a major diagnostic and therapeutic problem. In each instance, inadequate knowledge of the pathophysiology of chronic pain is a major impediment to the development of consistent and effective forms of therapy.

Endogenous Peptides - Endorphins: A most important step in the recent history of neuroscience research has been the discovery of specific opiate binding sites in the central nervous system and the subsequent discovery and chemical

identification of endogenous peptides which are apparently the natural ligands for those opiate receptors. Two pentapeptides were isolated from mammalian brain which have specific binding to the opiate receptors of the brain and differed from each other only in the 5th amino acid position: "Leucine" and "methionine-enkephalin". Subsequently, other larger peptides were found in the brain and pituitary with similar opiate binding capacity. The generic term "endorphins" was coined to encompass all such endogenous morphine-like compounds. The structure of methionine-enkephalin was found to be contained within a 91-amino acid pituitary hormone, beta-lipotropin, discovered some years earlier. Methionine-enkephalin occupied positions 61 to 65 of this longer peptide chain. It has now been shown that the entire 31-amino acid fragment comprising positions 61 to 61 of beta-lipotropin is itself a potent opiate receptor ligand, this peptide has been labeled "C-fragment" or "beta-endorphin". According to some workers beta-lipotropin may be a pro-hormone which becomes enzymatically cleaved in the pituitary or brain to form beta-endorphin and, in turn, methionine-enkephalin. On the other hand, it has been found that the quantity and distribution of beta-endorphin and enkephalin in the brain is unaffected by hypophysectomy. Also, no pro-hormone or other precursor has yet been discovered for leucine-enkephalin; so the possibility remains that beta-endorphin and the enkephalins, all of which have been found to exist intraneuronally in brain, are synthesized de novo and do not result from cleavage of still larger peptide chains.

These data on endorphins and those related to nociceptive modulation have links as follows: some are well confirmed while others need corroboration. Opiate binding sites, as well as enkephalin and beta-endorphin cell bodies and/or terminals have been found to be distributed in the brain in close proximity to each other and to medial brain stem sites known to support stimulus produced analgesia and the effects of minute injections of morphine on nociception. Beta-endorphin and the enkephalins have been found to have variable effects upon intraventricular injection or administration directly into the periaqueductal gray matter. Although the reason for the differences is not known, it seems possible that negative results are related to the fact that the enkephalins (unlike beta-endorphin) are enzymatically destroyed rapidly in the brain. Analgesic brain stimulation in the rat and in man has been reported to release measurable amounts of enkephalin-like material into brain tissue and cerebrospinal fluid. It has been reported that baseline endorphin levels are lower than normal in chronic pain patients, and that normal levels are restored by such analgesic treatments as transcutaneous electrical stimulation and stimulation of the medial brain stem.

It seems that there is considerable evidence suggesting the existence of a natural or endogenous antinociceptive or pain-inhibitory system having a specialized anatomy and a neurochemistry involving endogenous peptides. Yet reason and historical perspective compel caution. Many of the observations still need to be replicated and extended. We have already seen that multiple paths of modulation exist, some apparently related to opiate ligands and some not. Similarly, a causal link between dorsal horn neuronal inhibition and behaviorally defined analgesia is far from established, and a great deal of circuitry and synaptic neurochemistry of the modulation paths has yet to be disclosed. Moreover, there are several inconsistencies. In particular,

there is evidence that opiate drugs and endorphins can exert a direct antinociceptive action at the spinal level. Moreover opiate binding sites and endorphins are found in great density in those exact regions of the dorsal horn where pain inhibition is thought to take place.

Very little is known about the natural, physiological mechanisms which could act as accesses of control over the supposed endogenous pain-inhibitory system. There are data to suggest that endorphins are not released tonically under normal conditions but only when sustained discomfort or stress is experienced. It has also recently been reported that naloxone blocks placebo analgesia in placebo responsive human subjects. Whether or not any relationship exists between this finding and the reports of naloxone blocking acupuncture analgesia remains to be determined. Evidence examining the possible naloxone reversibility of some forms of analgesia is inconclusive. Until reliable data are available indicating the conditions under which the endogenous systems producing analgesia-like effects is entrained, it can scarcely be considered a true functional entity.

It is established that opiate binding sites and endorphins are located in brain areas apparently unrelated to pain inhibition. There are questions about the effects of opiates on sensory pain perception in clinically effective doses; therefore, opiate binding is not a certain link to the sensory aspects of pain. There are observations implicating the endorphins in such diverse pathological syndromes as psychosis, epilepsy, and dyskinesia or rigidity. There are suggestions that different opiate binding sites not only are anatomically separated but also differ from each other pharmacologically. Thus, it is evident that endorphins cannot be assigned a role exclusively in antinociception.

Treatment of Pain

There are four main modes of therapeutic approaches employed in the management for control of pain.

(1) Pharmacological Treatment: Alleviation of pain with minimum side effects produced by the drug is the main objective of this treatment. Drugs which are useful in the treatment of pain are classified into those which act peripherally at the tissue-receptor interface or on the receptors themselves and those which act at the level of the central nervous system. Some analgesics may act both peripherally and centrally; the site of action is not known for all analgesics.

Peripherally Acting Analgesics: The best example of a peripherally acting analgesic is aspirin. There is evidence that it has some central action as well. This common drug has the advantage of being both anti-inflammatory as well as analgesic. By virtue of its anti-inflammatory action, aspirin relieves a primary cause of pain by reducing the hyperemia, edema, and local tissue effects produced by the primary disease process and thus eliminates several potential sources of receptor activation.

Acetaminophen is less effective than aspirin in reducing inflammation and perhaps also in reducing receptor activation which accompanies tissue damage.

The mechanism of action of acetaminophen is not as well established as it is for aspirin. Although it is not a gastrointestinal irritant at high doses, it is also generally less effective than aspirin. Severe liver damage may occur as a result of overdose with acetaminophen.

Butazolidine, phenylbutazone and indomethacin are potent anti-inflammatory compounds which are used primarily in arthritic conditions or where pain can be relieved by directly attacking the inflammatory process. These are effective drugs but do not necessarily have a direct analgesic action in the absence of an inflammatory process. They are also potentially dangerous compounds because of their potential hematopoietic toxicity.

Phenoxybenzamine has been used effectively in some cases of causalgic pain due to peripheral nerve damage. This compound is an alpha adrenergic blocker and thus pharmacologically produces some of the effects of a sympathectomy. The difficulty with this compound is that the side effects (hypotension, lethargy, and decreased sexual activity) are often not well tolerated.

Propranolol is a beta adrenergic blocker used primarily in hypertension and cardiac arrhythmia. This drug has been found to be effective, however, as a prophylactic agent in many cases of migraine headache or other vascular headaches. This compound does not have primary analgesic effects; why it is sometimes effective in migraine and vascular headache is not known.

Centrally Acting Analgesics: The most effective and widely used central analgesics are the opium alkaloids of which morphine is the typical example. Most of the other commonly used narcotic agents are derivatives of morphine produced by various chemical substitutions on the morphine molecule or other alterations of its basic structure. The common examples are heroin, meperidine, codeine, and the weak narcotic agent propoxyphene. The more potent narcotics act at the central nervous system level to produce both an elevation of pain threshold and a euphoria which is particularly prominent in the case of patients suffering severe pain. Both the euphorogenic and sensory modifying actions of the narcotics are essential components of the analgesic action. The site of action of these compounds is not yet known but there is strong experimental evidence that their primary site of action in relieving pain is at the level of the reticular formation and deep structures closely associated with the reticular formation. The recent discovery of opiate receptors in the brain provides further evidence that these compounds act primarily at the level of the central gray substance and reticular formation in the upper brain stem; opiate receptors are also found in high concentration in the striatum, but there is no clear clinical or experimental evidence that this latter structure plays any significant role in pain or in pain modulation.

Morphine and the other opioid narcotics referred to above are capable of significantly depressing respiration, stimulating various smooth muscle structures, producing a deep narcosis, and predispose the patient to physical dependence and possible addictive use of these drugs. The addiction problem is undoubtedly related to the strong euphorogenic action of these compounds.

Nitrous oxide is another potent centrally acting compound which possesses strong euphorigenic and analgesic effects. The site of action of nitrous oxide is not known, but there is evidence that it may act on structures similar to those affected by morphine.

Anxiolytic agents such as diazepam and hydroxyzine are often useful in attenuating the motivational and emotional aspect of pain. In addition, these minor tranquilizing compounds, especially hydroxyzine, may strongly potentiate the action of morphine by mechanisms as yet unknown. Major tranquilizers, such as the phenothiazines, may also potentiate the action of morphine and they may be used in conjunction with the weaker narcotics such as propoxyphene. This latter combination has been found particularly useful in the treatment of painful neuropathies.

Lithium has been found useful in the prophylactic management of cluster migraine. There is no evidence at present that lithium has a primary analgesic action of its own. Its mode of action in the prevention of cluster headache is unknown.

Other centrally acting compounds which may be of particular benefit in pain due to disease of the nervous system include carbamazepine, phenytoin, and other anticonvulsant medications. These drugs are frequently successful in controlling tic douloureux and various types of central pain.

Future Trends: Development of peripherally acting compounds which can selectively attenuate pain without interfering with other sensory modalities: The identification of specific algogenic substance(s) in tissue and mechanism by which they activate nociceptors. The identification of those regions of the nervous system which are primarily concerned with mediating the experience of pain. Development of drugs which specifically interfere with transmission along the pathways or to selectively trigger descending pain modulatory systems. Identification, distribution and elucidation of function of endogenous opioid peptides (enkephalins) and to use these peptides in the alleviation of pathological pain.

(2) Physical methods: The variety of physical and physico-chemical therapeutic techniques in current use for the relief of pain include: diagnostic and therapeutic nerve blocks, physical therapy, electrical stimulation of skin, and acupuncture.

Nerve blocks for pain therapy: Nerve or analgesic blocks, in which a local anesthetic or neurolytic agent is injected in or around a site of nerves or pain-sensitive structures have been used to control acute and chronic pain for about a century. Experienced clinicians can block virtually any nerve in the body which contains pain pathways. The basis for the efficacy of nerve blocks in patients with pain is the interruption of specific sensory pathways for pain, sympathetic motor nerves, and somatic motor nerves. Blocking pain pathways relieves pain promptly and interrupts the sensory side of abnormal reflex mechanisms which may be contributing to the physiopathology of the pain syndrome. Blocking sympathetic pathways eliminates the increased vasomotor, sudomotor and visceromotor hyperactivity which often contributes to the physiopathology of certain pain syndromes such as causalgia, reflex

sympathetic dystrophies and visceral pain. Blocking somatic motor nerves relieves muscle spasm which is often associated with musculoskeletal disorders and contributes to the painful stimulation. Low concentrations of local anesthetics block the A delta and C fibers without significantly affecting motor functions.

Physical therapy: The empirical use of heat and cold, especially heat, to relieve pain is probably as old as mankind. Studies in recent years have shown that when heat, either in the form of infrared radiation or ultrasound, is applied to the skin overlying a major nerve or painful area, the pain threshold increases. For chronic pain states, it is best to use high temperatures--43-45° C.--applied to the site of pathology. This usually produces relief. For acute pain of bursitis or herniated discs, it is preferable to apply milder temperature ranges for superficial relief. In many conditions it is more appropriate to apply cold. Physical exercise and postural manipulations are also used to treat or prevent pain. They are very effective when lumbar lordosis is a cause or aggravating factor in low back pain. The patient with exaggerated lordosis and accompanying increased forward (downward) thrust of the pelvis develops contracture or shortening of the spinal extensors and hip flexors. The abdominal muscles and hip extensors, which normally act as a force couple to tilt the pelvis backward (upward), may be weak. Flexion exercises are designed to stretch the spinal extensors and hip flexors, and to strengthen the abdominals and hip extensors. The patient is taught to press the pelvis backward to decrease the lumbar lordosis, first while in a supine position and then while sitting, standing and walking. Exercise is also indicated in treating patients with chronic pain due to other musculoskeletal disorders, particularly those affecting the limbs and neck. These include chronic myofascial pain syndromes, postoperative pain and disability, chronic reflex sympathetic dystrophy, and patients with chronic pain behavior due to operant mechanisms. Traction is most frequently applied to the cervical spine. It can provide significant relief of pain and relieves pressure on compromised nerve roots. Moreover, the pain relief often far outlasts the duration of traction. Why this should be so is not completely understood, but is probably due to separation of the vertebrae which, while minimal, increases the size of the intervertebral foramina. Studies have shown that maximal separation requires the application of traction for at least 25 minutes at a force sufficient to achieve vertebral separation. It is helpful to use heat massage to relax the involved muscles and prevent voluntary contractions which can overcome traction of up to 55 pounds. The rationale for manipulation is the least well established of the physical treatment modalities. Many individuals are seeking manipulative therapy. This suggests that some unknown mechanism is involved in skeletal-neuromuscular relief of pain, even though the scientific explanation is lacking.

Transcutaneous electrical stimulation: For hundreds of years patients, physicians, and charlatans have played with electricity as a form of therapy for all kinds of illness, including pain. The mode of action of electrical

stimulation is unknown. The fact that a significant number of patients can be benefited justifies its use as a clinical tool. Electrical stimulation of the skin is now a safe and inexpensive method of alleviating pain in some patients. This technological advance is the result of the development of compact, lightweight, battery-operated, solid-state devices. The major problem with transcutaneous electrical stimulation (TES) is patient selection. No valid predictors of long-term efficacy have been found. Some generalizations are possible, based on studies over the past decade: Electrical stimulation is not effective in patients with markedly abnormal or absent sensation in the region stimulated. Pain relief is usually reported only when paresthesia is elicited in the area of pain. Approximately three-fourths of an unselected group of chronic pain patients will report initial pain relief with TES, but only one-fourth will report significant pain relief lasting more than three months. Some of this pain relief may be ascribed to non-specific effects (placebo), but some is clearly related to the sensory effects of stimulation.

Acupuncture: In China, the use of acupuncture for the treatment of acute and chronic pain dates back several millennia. While there have been modifications in the concept, in the number of acupuncture points, and even in techniques over this period, it has never been abandoned. Today, therapeutic acupuncture in China is used extensively to relieve nearly all types of painful conditions. Despite the long and widespread use of acupuncture and claims of its great efficacy in treating pain and other non-surgical disorders, no strong evidence is in support of this claim.

(3) Surgical control of pain: Interruption of those pathways in the nervous system which are concerned with pain is a logical approach to the relief of intractable pain. This is especially true when powerful analgesic-narcotic drugs are ineffectual, either initially or as a result of the development of tolerance. Surgery for pain has in the past been considered a last resort, not because of intrinsic shortcomings, which exist, but because of the risk associated with surgery and the realization that severing central pathways is an irrevocable step. Nerve cells and fibers in the brain and spinal cord cannot regenerate. That surgery can provide relief from some of the most severe and disabling human pain is well established. The paroxysmal bursts of intense searing facial pain of tic douloureux, for example, can be permanently relieved by surgery. Moreover, the newest techniques provide pain relief while sparing other facial sensibility. The persistent, progressively severe pain which often parallels the spread of cancer can be controlled for periods of six months to a year by interrupting the main pain pathway in the spinal cord. Thus, this procedure (spinothalamic cordotomy) provides pain relief exactly when it is most needed.

In the search for better methods of controlling pain, progressively higher levels of the nervous system have been explored in efforts to relieve pain or the anguish, fear, and suffering which accompanies pain. It is at this point that the issue of psychosurgery arises, for surgical intervention may affect the personality or other uniquely human quality of the individual. Improvements in the techniques of psychosurgery, whereby impairments in personality are completely or almost completely avoided, while anguish and suffering secondary to pain are controlled, might clearly benefit some

patients. Such surgery would eliminate the psychological influences on the patient even though pain, as such, might not be modified. Such procedures must always be evaluated in the context of the severe, incapacitating and at times overwhelming magnitude of the pain problem confronting the patient and the family. Psychosurgical procedures for pain must be evaluated in an effort to reach a balanced and objective position. Benefits far outweighing the shortcomings can be derived from specific psychosurgical procedures in a small number of selected cases, provided that ethical safeguards are assured the patient and treatment is undertaken by highly qualified surgeons.

(4) Psychological techniques: The psychological techniques currently employed to relieve acute and chronic pain include: 1) psychotherapy, 2) bio-feedback, 3) hypnosis, and 4) operant conditioning and related methods of behavior modification. These generally unrelated modalities are all considered "psychological" techniques because pain relief is achieved primarily by altering psychological, motivational or cognitive factors by psychologically induced changes in autonomic or somatic functions, or both.

Future Outlook in Pain Research: Few areas of research endeavor touch upon so wide a range of significant problems in basic and clinical neuroscience. The biophysical and biochemical mechanisms of a unique class of receptors are to be investigated. Noxious stimuli are potent activators of a broad range of somatic, autonomic and neuroendocrine reflexes, the organizations of which are in the very early stages of investigation. Our understanding of sensory physiology, and the neural coding systems requires continued research on pain mechanisms. The activation of nociceptive afferents offers a uniquely effective way of engaging the neural systems which subserve attention, motivational and affective states, and provide a necessary condition for learning. Pain is a major, dominant component of a wide variety of clinical disorders and, especially in its chronic form, it presents a crippling burden to the society for the patient's care. There continue to be significant advances in the assessment, treatment, and management of pain based in large part upon an improved understanding of pain mechanisms. But many of the current treatments for pain are of doubtful value and some carry a significant risk of morbidity, if not mortality. Promising avenues of approach need to be explored. The present deficiencies in pain management can be attributed to lack of basic knowledge about the pathophysiology of pain, the failure to communicate what is known to the health care community, and the misapplication of current knowledge in the clinical setting.

Minimal Brain Dysfunction

Minimal brain dysfunction (MBD) is recognized to be one of the most pressing problems in contemporary medical practice affecting an estimated 5-10% of the school age population. Clinically the disorder exhibits certain cardinal features which include: onset in early life and evolving clinical picture throughout childhood; involuntary hyperactivity which completely surpasses normal-hyperactivity, however, which disappears or abates as the child approaches adolescence; evidence of impaired cognitive performance; and inability to adjust to changes in the environment.

Of particular interest is the evidence from several lines of investigation which supports the notion that many of the features of the MBD syndrome may be related to brain catecholaminergic mechanisms. Administration of amphetamine, or the closely related stimulant, methylphenidate, to many children with MBD often results in a pronounced decrease in motor activity and improvement in tests of performance. Pharmacologic data suggest that central catecholaminergic systems mediate the actions of amphetamine, and since amphetamines appear to affect the symptoms of MBD, central catecholaminergic systems might be related to the symptoms of MBD.

Recent clinical studies involving the determination of monoamine metabolites in CSF lend support to the belief that central catecholaminergic systems may play a role in MBD. Considerable experimental evidence suggests that the concentration in CSF of 5-hydroxyindole acetic acid (5-HIAA) and homovanillic acid (HVA), the major metabolites of serotonin and dopamine, respectively, reflect the activity of their parent amines in brain. Administration of amphetamine resulted in significant alterations in CSF concentrations of HVA but not 5-HIAA in hyperactive youngsters. This is interpreted as supporting an abnormality in central dopaminergic function in children with hyperkinesis. Utilizing the probenecid loading technique, it was found that HVA in children with MBD was significantly reduced compared to controls, but 5-HIAA was not altered. Thus, these findings like those above, suggest that central dopaminergic (DA) systems play an important role in MBD rather than serotonergic systems.

It was therefore believed that, along with other unknown etiological factors, MBD is caused by the excessive accumulation or production of dopamine in the early stages of development, and if some way could be found either to deplete or interrupt its production by inhibiting the enzymes that produce it, one could develop a rational basis for treatment of hyperactive and dyslexic children. These suggestions, based upon previous observations, prompted the investigators to develop a 6-hydroxydopamine (6-OHDA) treated rat-pups model for investigations of MBD. Using these manipulations specific central DA pathways were lesioned in neonatal rats by 6-OHDA, and a number of similarities between the development profile of rat pups depleted of brain dopamine and certain cardinal symptoms in the clinical syndrome of MBD in children have been observed.

The selective reduction of brain dopamine produced by the intracisternal administration of 6-OHDA to 5 day old rat pups results in a developmental pattern that has many parallels with the clinical syndrome of MBD observed in children. Rat pups treated with 6-OHDA as neonates are significantly more active than their littermate controls during the period of behavioral arousal that occurs between two-three weeks of age. However, as the rat pups approach maturity the hyperactivity initially observed in the 6-OHDA treated animals is no longer apparent. This finding appears to correspond to that found in children with the clinical syndrome of MBD. In these affected youngsters hyperactivity is pronounced until 10-12 years of age, but then abates, and is similar to that seen in the experimental model of hyperactivity in rats. Furthermore, in children with MBD, although the hyperactivity does disappear, associated cognitive difficulties frequently persist. Similarly, rat pups depleted of brain dopamine as neonates have in addition, deficits in learning, as demonstrated by the persistently impaired performance in both the T-maze and shuttle box avoidance tasks. As noted above, administration of stimulant medications such as amphetamine or methylphenidate to children with MBD frequently results in a diminution of hyperactivity. Rat pups depleted of brain dopamine respond in a similar fashion with attenuation of activity levels and significant improvement of avoidance performance. Still another parallel may be found in the response of both children with MBD and 6-OHDA treated rat pups to a sudden alteration in the environment. For a child with MBD, any change in milieu all too often results in an exacerbation of both hyperactivity and distractibility. This inability to adjust well to change has its counterpart in the impaired ability of 6-OHDA treated rat pups to modulate their activity when placed in a new environment; an effect described experimentally as habituation of activity.

In the future specific central DA pathways will be lesioned in neonatal rats by 6-OHDA. The accuracy, magnitude, and specificity of the destruction of cell bodies in the nigrostriatal and mesolimbic systems will be determined by chemical analysis of DA levels in the striatum, nucleus accumbens, and olfactory tubercle. Behavioral measurements, following 6-OHDA treatment will be correlated with residual concentrations of DA, NE, HVA, catechol-O-methyl transferase, and catecholamine turnover. Among the brain areas to be studied are the hypothalamus, hippocampus, pons, and medulla. Some of the behavioral activities will be monitored and compared with those of the control animals.

Attempts will be made to reverse some of these behavioral anomalies by using medication commonly employed in treating MBD, namely amphetamine and methylphenidate together with other drugs such as apomorphine (a DA agonist), haloperidol (DA antagonist), bromocryptine (agonist), and clonidine (NE agonist)

REYE'S SYNDROME (RS)

Reye's Syndrome is a sudden and fulminant disease of childhood characterized by hyperammonemia, encephalopathy and massive fatty infiltration of the viscera, especially the liver. Characteristically, the disease is preceded by a prodromal viral infection, of a few days duration, which is most often influenza B or varicella. Recovery from the prodrome is usually followed by onset of intractable vomiting, hepatomegaly and signs of rapidly progressive cerebral edema. In approximately 40 per cent of cases, the encephalopathy proceeds to the extent of irreversible brain stem damage and even death, often within 24-48 hours from onset of the acute phase of this disease. However, in areas where special treatment teams are available, mortality rates have been reduced to approximately 20%. The Center for Disease Control (CDC) has estimated that Reye's syndrome has become the leading cause of virus-associated central nervous system disease in individuals from 0 to 24 years old. Epidemiological studies at the CDC have demonstrated that the disease in the United States appears to be concentrated in a southwest to northeast band which includes New York State.

Etiology: Most authorities agree that a non-specific virus is involved in the prodromal phase of the disease. Superimposition of another more specific virus or of more specific toxins such as aflatoxin, hypoglycin or insecticides (and their solvents) have been suggested as complicating and/or contributing factors. Inborn errors of metabolism have also been mentioned as a possibility predisposing to this disease. Accidental poisonings by the agents mentioned can never be completely eliminated. From a consideration of these possible etiologic conditions leading to the Reye's Syndrome, one must conclude that viable, post-insult therapy will continue to be needed until satisfactory management of such patients is attained. The greatest chance for successful prophylactic control of this disease lies in the possibility that an environmental influence or toxin might be implicated, identified and eliminated. However, the highly sporadic nature of the disease is often offered as an argument against this possibility. If environmental manipulations are not the key to prevention and no secondary infectious agent can be isolated, one is left with the requirement for an effective treatment as essential to the control of this disease.

Pathology: The clinical course of RS begins with intractable vomiting and lethargy, and proceeds through rapid deterioration of neurological function. Patients with RS usually have high concentrations of serum ammonia, high serum transaminase activity, and prolonged prothrombin times which originally suggested a hepatic basis for the encephalopathy. However, more recent evidence suggests that impaired liver function alone may not be the primary basis for the illness. In some cases, the CNS symptoms precede evidence of hepatic involvement. High serum concentrations of creatinine phosphokinase indicate that muscle may be affected. Fatty degeneration occurs in several of the viscera, not just liver. Morphological examination of biopsies from RS patients have shown structural alterations in mitochondria from liver, brain, and skeletal muscle. The suggestion that an accumulating metabolite or an exogenous toxin may be causing cellular damage has been made repeatedly.

Animal Model and Biochemical Correlates: Fatty acid metabolism: High values of circulating blood ammonia are characteristic of the acute phase of Reye's Syndrome. The hyperammonemia may be secondary to a fatty acidemia, possibly as a consequence of disruption of hepatic mitochondrial metabolism and associated urea cycle activity. Some of the published etiologic models, for example, aminopentenoic acid intoxication, have led to simultaneous elevation of serum free fatty acids and ammonia. The latter two substances may act synergistically in the induction of experimental coma.

Clinical findings on the levels of serum free fatty acids in children with Reye's Syndrome indicated increased levels (up to 30 fold) of long chain fatty acids in acute phase sera from such patients. A biochemical manipulation is being sought to deal therapeutically with this elevation of free fatty acids. In order to explore such a rationale, the intoxication of rats with fatty acids was examined. Because of the experimental difficulties in solubilization and absorption of long chain fatty acids, a short chain fatty acid (SCFA), sodium octanoate, was used in a rat model.

With these manipulations, results from this pilot study indicated that the coma inducing effects of sodium octanoate could be modified or eliminated by the concomitant or subsequent injection of D, L-carnitine. Rats given sodium octanoate remained unconscious as measured by absence of the righting reflex for approximately 35 minutes. Injection of D, L-carnitine one minute after the onset of coma reduced the period of unconsciousness by approximately 50 per cent. A simultaneous injection of carnitine either substantially reduced or prevented the period of coma.

Carnitine was chosen as a potential therapeutic agent for octanoate-induced toxicity because it is known to promote the metabolism of various fatty acids by enhancing transport of such compounds across the mitochondrial membrane. Such enhancement of fatty acid transport is more effective for long chain fatty acids than short chain fatty acids, the SCFA possessing the ability to traverse the mitochondrial membrane by simple diffusion. Carnitine also reverses the effects of hypoglycin analogs in rats, and has also been reported to effectively antagonize acute alcohol-induced triglyceride accumulation in rat liver. Rats on a diet devoid of carnitine or its metabolic precursor, lysine, develop fatty infiltration of the liver. The report of elevated plasma levels of lysine in children with Reye's Syndrome suggests a possible defect in carnitine synthesis. All of these findings supported choice of carnitine as a possible antagonist to octanoate toxicity. In addition to the anticipated effects of carnitine on fatty acid metabolism, it is postulated that carnitine might also be of use in interrupting positive feedback loops that might be present if the fatty acidemia was secondary to other blood derangements. Thus, a sequence of a) urea cycle derangement, b) increased blood ammonia, c) fatty acidemia, d) hepatocellular fatty acid infiltration, and e) mitochondrial damage, all of which would lead to further urea cycle derangement, might possibly be interrupted if the fatty acids could be rapidly cleared by hepatic tissue. These and other possibilities can be examined with the establishment of the animal model based on such a hypothetical pathogenesis.

Mitochondrial Impairment and Serum Factor: Morphological examination of biopsies from RS patients have shown structural alterations in mitochondria from liver, brain and skeletal muscle. On the basis of these observations it was decided to investigate the hypothesis that a "serum factor" may be responsible for the mitochondrial damage seen in RS. Rat liver mitochondria were isolated and assessed for classical parameters of respiratory function in vitro in the presence or absence of RS serum. Using this general approach it was possible to demonstrate an inhibitory effect of RS serum on the oxidative metabolism of isolated rat liver mitochondria. Serum from normal donors or from comatose patients with chronic cirrhosis, autoimmune disease (lupus erythematosus), or with chronic active liver disease (microcystic) had no effect on mitochondrial function. Also serum from RS patients after "total body washout" or exchange transfusion or both did not change mitochondrial functions. The results suggested the existence of a serum factor which might be important in the pathogenesis of RS. Further studies investigate the hypothesis that the putative serum factor is important in the pathogenesis of RS serum affecting energy-linked functions such as cellular respiration, fatty acid oxidation, urea synthesis, protein synthesis, and glycolysis. An attempt will be made to define the chemical identity of this factor and the potential usefulness of the biochemical assays as a diagnostic test for the presence of RS factor will be explored.

Monoamines and Reye's Syndrome: Evidence from several lines of investigation suggests that brain edema plays a vital role in RS. Numerous reports have emphasized that brain weight is increased. At autopsy, the cortical gyri are flattened, the ventricles are decreased in size, and tonsillar coning is present, suggesting brain edema. On clinical grounds, cerebrospinal fluid pressure is frequently increased, particularly in children who subsequently die. Despite this compelling evidence of brain edema in RS, little is known of the mechanisms involved. Continuous intraventricular monitoring in the management of Reye's Syndrome provided the opportunity to define some of the factors influencing the development of brain edema. In particular the concentrations of the metabolites of serotonin (5-hydroxyindoleacetic acid, 5-HIAA) and dopamine (homovanillic acid, HVA) in the ventricular fluid were examined. A markedly increased concentration of homovanillic acid during the early period of brain edema in RS was found. The elevated concentrations of HVA in children with RS supports the idea that brain monoaminergic systems may be involved in the genesis of this disorder. The results suggested that cerebral dopamine, rather than serotonergic, mechanisms are most important, since 5-HIAA was unchanged. It is possible that an undefined metabolic insult may initiate cerebral ischemia. Restriction of oxygen supply may induce brain edema. Another consequence may be the release of vasoactive amines into the brain, acting locally to constrict cerebral vessels and exacerbating the damage. If therapeutic measures interrupt this sequence, it may be possible to ameliorate some of the consequences. Therapy might include pharmacologic agents that prevent release of amines or block their actions on receptors. Whether such medication would affect the course of Reye's Syndrome remains to be investigated.

Neuropsychological Consequences of Reye's Syndrome: With increased number of children recovering from the acute encephalopathy of Reye's Syndrome, the need for more information on the neuropsychological sequelae from the disorder becomes urgent. Available data concerning other CNS disorders suggest that a range of disabilities might be anticipated. Over one hundred patients recovering from Reye's Syndrome have been examined. Preliminary findings suggest a highly variable outcome in that IQs ranged from less than 50 to over 100 in moderate to severe cases. Measured IQ scores are not sufficient for indicating the extent of damage resulting from conditions affecting the central nervous system. Therefore, the necessity for using a wider range of more sensitive cognitive, language, and perceptual-motor measures in assessing outcome of treatment is apparent.

Future studies are directed to establish the level and types of neuropsychological deficits immediately following the acute phase of illness. Efforts will be made to determine the relationship between diagnostic laboratory findings, clinical or neurological findings, and the rate and pattern of recovery in neuropsychological functions, i.e., cognitive, language, perceptual-motor and motor functions by follow-up evaluations at 12 months and 24 months. Parents' understanding of the etiology, prognosis, and sequelae of the syndrome as well as their perception of the impact on the family immediately, and at follow-up will be assessed. The nature and priority of rehabilitative needs will be identified as perceived by the family and, when possible, by the patient.

Treatment: Early treatment has been combined with prompt institution of a standardized regimen of supportive therapy and exchange transfusion in all patients with severe or rapidly progressive disease. General supportive measures currently being employed are as follows: (1) 24 hour maintenance of fluid and electrolytes with 10-15% glucose; (2) maintain airway and avoid anoxia; (3) elective endotracheal intubation if anticonvulsants are used; (4) mannitol over 30 minutes or less to reduce cerebral edema; (5) vitamin K, (6) type and cross-match; hold blood in readiness for exchange transfusion; (7) correct electrolyte imbalances while monitoring urine flow; and (8) constant intensive nursing.

Parkinson's Disease and Parkinsonism

The diseases of childhood are anticipated with resignation by every parent who knows that children must pass through the necessary quotas of childhood infectious diseases. The diseases of aging are much more ominous in their approach and are thought to herald the end of the life cycle rather than the beginning. Parkinson's disease, the most common form of parkinsonism, is an illness almost unique to those over the age of 50. About one-half million people in the United States are affected by Parkinson's disease, or about 1% of the population over age 50. Prevalence and incidence rates remain the same in all races and throughout the world where good epidemiological studies have been conducted. Men and women are equally affected.

Strong evidence now supports the findings that Parkinson's disease is not hereditary nor is it the product of an environmental toxin or pollutant. A large study of monozygotic twins, one of each set with Parkinson's disease, was conducted by investigators at Mt. Sinai Hospital in New York. The study demonstrated that in no instance were both twins of a set affected. There is also no evidence that offspring of Parkinson's disease patients have a greater risk of developing the illness than anyone else. Since husbands and wives share similar environments, it is not likely that a dietary or environmental pollutant is the origin.

Whatever does cause Parkinson's disease remains a mystery. Dopamine containing neurons in the substantia nigra die, causing a depletion of this important neurotransmitter. Gradually, clinical signs of tremor, rigidity, and bradykinesia begin to appear, becoming more severe as time passes. Many patients suffer gradually diminished intellectual faculties. The symptoms of parkinsonism can result from neuroleptic administration, as a postencephalitic sequelae, from arteriosclerosis and from a variety of diseases and intoxications.

The majority of grants on Parkinson's disease focus on the biochemistry of the illness and the ways in which neurotransmitter systems transmit messages in the brain areas most affected. It is not surprising that the biochemistry of this disorder should preoccupy scientific attention; after all, discoveries about the deficiencies of dopamine in Parkinson's disease patients led to breakthroughs in our understanding of neurochemistry and pharmacology in brain disorders in general.

Now that the initial excitement of discovering that decreased dopamine stores leads to the symptomatology known as parkinsonism has subsided, it has become increasingly apparent that administration of L-dopa to increase endogenous dopamine stores is not sufficient to treat the disease completely. Unpleasant side effects and an erratic effectiveness of the treatment, known as the "on-off" phenomenon has pushed scientists to develop new treatments. Many of these compounds act in concert with L-dopa to increase its potency. Investigators at New York University have been trying two dopamine agonists in particular, ergot derivatives lergotrile and bromocriptine, in patients with Parkinson's disease, and in monkeys with unilateral lesions in the ventromedial areas of the brain stem which serve as useful animal

models for evaluating drug efficacy. A clinical trial of lergotrile mesylate given with levodopa combined with carbidopa, revealed that abnormal involuntary movements were decreased on addition of lergotrile and reduction in levodopa, while mental changes and orthostatic hypotension were increased. The effects of stress on epinephrine and norepinephrine neuronal systems, the occurrence of a somatostatin-like immunoreactivity in some peripheral sympathetic noradrenergic neurons, and the interactions of bromocriptine and lergotrile with dopamine and adrenergic receptors are also being explored.

At neighboring Yeshiva University in New York, other investigators in a Center research program are also studying the role of biogenic amines in neurological disorders. Clinical and basic research studies at the Center are aimed at further elucidating the dopamine (DA) neuronal receptor system. These investigators have pharmacological evidence of three types of dopamine adenylate cyclase receptors in the striatum, anterior limbic cortex, and frontal cortex. Ligand binding studies are being carried out within parts of the extrapyramidal system to determine the properties of the dopamine adenylate cyclase receptors, including supersensitivity and subsensitivity. Explorations will be made of the behavioral effects in rats with denervation supersensitivity after nigrostriatal lesioning. As part of a project to study the dopamine system as a whole and its interactions with other neuronal systems, the effects on the DA neuronal system of peptide transmitters and GABA will be examined. The investigators are using a variety of sophisticated techniques including 2-Deoxyglucose autoradiography and histofluorescence to learn more about the sites of action of DA agonists and the anatomy and processes of DA cells. Clinical studies will include patients with other diseases which affect aminergic activity, such as Tourette's syndrome, tardive dyskinesia, action myoclonus, and others.

Cornell University in New York City is carrying on another large program project grant with many pharmacological studies aimed at developing new and improved treatments for parkinsonism. A variety of dopamine agonists and analogs such as N-propylnorapomorphine (NPA), will be examined as well as the effects of current levodopa treatments on immune functions, hormonal metabolism, and behavior. Pharmacological and biochemical studies are being conducted both in Parkinson's disease patients and in animal models.

In order to improve the therapeutic efficacy of existing treatments for Parkinson's disease, investigators at the Illinois Institute of Technology are experimenting with the use of metal chelates bound to L-dopa as an aid to transporting the amino acid across the blood-brain barrier. At the University of Rochester, other scientists are exploring the effects of chronic levodopa, phenobarbital, and diphenylhydantoin administration on the gastrointestinal tract, since these drugs are absorbed in large part by the gastric mucosa prior to reaching their effective sites in the brain. The structural and functional studies being carried out may give insight into the toxic side effects of these drugs and possible adverse effects of taking them in combination.

Another Center for the study of Basal Ganglia Disorders and Neurotransmitter Function, at the University of Colorado, supports interdisciplinary basic

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and clinical studies aimed at discovering the interplay among cholinergic, dopaminergic, and other neurotransmitter systems with a view toward eliminating adverse treatment effects, such as the "on-off" phenomenon in Parkinson's disease, and tardive dyskinesia.

While some investigators are involved with understanding and improving upon current therapeutic regimens for Parkinson's disease, other scientists are looking more broadly and basically at the neurochemical, histological, and anatomical systems of the brain which are most affected in Parkinson's disease and related basal ganglia disorders. At the University of California at San Diego, a research program is mounted to analyse the organization of monoamine neuron systems in the mammalian brain and their response to injury. The maturation of the catecholamine neuron system and its plasticity in response to drug induced and mechanical damage during development and in maturity is being examined.

Neurotransmitter function in the globus pallidus of monkeys is the target of investigation for scientists at the University of Texas. The effects of acetylcholine (weak to moderate excitant), dopamine (weak excitant), serotonin and substance P (little or no effect), gamma-aminobutyric acid (strong inhibitor), taurine, glycine, and beta-alanine (inhibitors) on the responsiveness of neurons in the globus pallidus are being measured to determine normative functioning in an area of the brain damaged by a number of extrapyramidal disorders.

The substantia nigra is the object of study for another investigator at the University of California in Los Angeles. The objective of this research is to determine the cytoarchitecture, projection patterns, and functional significance of acetylcholinesterase (AChE) containing neurons in the substantia nigra. This research group has already presented evidence that AChE is contained within the dopamine neurons in the pars compacta of the substantia nigra, possibly to inactivate acetylcholine released from cholinergic afferents to the nigra. Understanding cholinergic-monoaminergic interactions in the nigra may improve our comprehension of the role of the substantia nigra in Parkinson's and Huntington's disease.

Chemical lesioning gives much information about the "wiring diagram" of the basal ganglia, but electrophysiological and anatomical techniques are equally valuable. Scientists at the University of Washington are examining the neurons of the entopeduncular nucleus (ENT) and describing afferents to and efferents from this area, as well as the synaptic actions of ENT cells of several brainstem sites which may link the ENT to the globus pallidus. The investigators seek to clarify what drives the high tonic firing rate characteristic of pallidal and nigral basal ganglia output neurons in awake animals.

Scientists at the VA Lakeside Hospital have made an animal model of Parkinson's disease by lesioning the nigrostriatal pathway in cats and are studying neurotransmitter balance in the caudate nucleus of the lesioned animal. Their theory is that Parkinson's disease results from an imbalance among the cholinergic, dopaminergic, gabanergic, and serotonergic systems

enervating this area.

Other investigators are pursuing a variety of other biochemical studies, looking at the pharmacological effects and metabolism of apomorphine alkaloids and apomorphine itself, the role of cyclic AMP in regulating catecholamine synthesis, and the influence of endocrinological factors such as melanocyte-stimulating hormone (MSH) and MSH-inhibiting factor (MIF) on systems involved in Parkinson's disease and mental depression. Some neurophysiological studies underway are aimed at learning more about the development of the extrapyramidal system in an opossum model, and the capacity of selected brain parts in rats to recover function after lesioning.

In Fiscal Year 1979, the Neurological Disorders Program received 32 applications of which 21 were approved and 11 funded totaling \$712,234 (direct costs only).

Huntington's Disease

Huntington's disease is a disorder of the basal ganglia closely related to Parkinson's disease. While parkinsonism produces tremor and rigidity, Huntington's disease causes uncontrollable chorea, and gradual loss of the capacity to ambulate. Patients are dysarthric, and the majority show some degree of dementia, usually severe toward the end of the illness. Profound emotional disturbances may also occur. Huntington's disease is transmitted as an autosomal dominant gene and usually manifests itself between the ages of 35 and 40 years. Children comprise 10% of cases. Treatment is merely palliative and most often entails the administration of dopamine blockers or antagonists. There is no test to determine which child of a Huntington's disease patient is carrying the lethal gene before symptoms of the illness appear. Patients generally live 10 to 20 years following symptom onset. Biochemically, the disease is characterized by reduced stores of GABA and glutamic acid decarboxylase (GAD), ACh, substance P, angiotensin II converting enzyme and a variety of other neurotransmitters and neuromodulators. There is almost total loss of the small neurons of the caudate nucleus and putamen as well as cortical atrophy, giving rise to a typical picture of enlarged ventricles and sulci on CAT scans.

A number of investigators are attempting to identify the abnormal gene that is responsible for the host of physical and mental symptomatology that characterizes Huntington's disease. Based on the genetic prediction that a mutant protein would produce an abnormal charge or weight compared to its homologous gene, and that this difference could be detected through the use of 2-dimensional gel electrophoresis, a scientist at the City of Hope National Medical Center in Duarte, California, has been screening over 2,000 gels from multiple brain areas, fibroblasts, red blood cells, and other non-neural tissues. An abnormal double major spot with two satellite spots was finally located in a perchloric acid extract of the putamen and caudate of an HD patient. A similar mutant protein was found in the brains of some patients with classical schizophrenia but not with other neurological diseases. Controls did not have this protein, nor did all HD patients. The investigator has hypothesized that HD and schizophrenia may be allelic variations of the same gene. Work is now being carried out to isolate and characterize these mutant proteins and test for their presence in a larger sample of patients with different disorders.

Another way to locate the HD gene is to search for a marker in close proximity to it on the chromosome. Investigators at the University of Rochester are looking for possible linkage or allelism of the genes for plasma cholinesterase (E1 and E2) and Huntington's disease. The study stemmed from a report from Britain that there is an increased incidence of the rare E1 gene and C5+ variant of cholinesterase in HD patients. The association may be due to actual linkage or to the modification of the expression of the gene. This research may offer clues as to future research directions, including early diagnosis and treatment.

For many years, Huntington's disease has been considered strictly a brain disorder. In recent times, however, the question arose as to whether the

HD gene might produce modifications of non-neural tissue. Scientists from the University of Kentucky have been in the forefront of demonstrating that the HD gene may well cause a generalized membrane defect. Subjecting erythrocyte ghosts to analysis by electron spin resonance, scientists have discovered an alteration in the physical state of membrane proteins in HD patients, as compared to normals and other neurologic disease controls. The W/S ratio was altered in HD patients and HD red blood cells showed an increased tendency to form stomatocytes. Increased sialic acid was also noted in the HD erythrocyte membranes. A thorough investigation of these findings, using ESR, gas-chromatography mass spectrometry, scanning electron-microscopy and enzymatic analyses is now in progress.

Other indications that HD might involve a generalized membrane defect have come from studies of skin fibroblasts. Fibroblasts have been found to grow to increased cell densities at confluence and have a decreased growth rate after a certain number of passages. Investigators at the University of Oklahoma are exploring biochemical alterations in fibroblasts from HD patients. GAD activity and GABA pool size is abnormal in HD fibroblasts. The uptake and kinetics of neurotransmitters in the fibroblast cultures are being compared with neuronal cultures. This technique may provide a "window" on brain functioning and permit a variety of studies not ethically possible now.

Fibroblasts have also been examined for decreased peroxidase levels or activity which could lead to a damaging accumulation of lipopigments. A variety of studies using cell cultures both from HD patients and from persons with Batten's disease are being pursued at Stony Brook University of New York.

Ever since the revolutionary work of Gajdusek and Gibbs pushed scientists to consider more unconventional etiologies for chronic degenerative neurological disease, the role of virology and immunology in neurologic disease has received increased attention. It is certainly conceivable that a virus could become integrated into the genome to produce the symptoms and Mendelian inheritance pattern of Huntington's disease. A scientist at the University of California is attempting to explore this hypothesis. His current work is aimed at characterizing a cellular immune response in HD patients which was discovered in his laboratory. Using the mixed lymphocyte inhibition (MLF) assay, this scientist discovered that lymphocytes from HD patients appear to be immunologically sensitized to HD brain tissue, but not to brain tissue from normals or other patients. This finding may be due to the leakage of antigens through the bloodbrain barrier due to brain deterioration or to the presence of a possible specific HD brain antigen.

Animal models have always been important in the understanding of the etiology, pathogenesis, and possible treatment of disease. HD is no exception. Very recently, a new animal model was created by the injection of kainic acid, a powerful glutamate analogue, into the striatum of rats. The kainic acid produces a selective degeneration of striatal intrinsic neurons and neurochemical and histologic alterations in the nigro-striatal circuit that closely mimics those found in HD. Fibers of passage are not affected by the kainate, and the chemical has no effect if cortical-striatal pathways

are severed. Further studies are now in progress to determine the means by which kainic acid exerts its effects and to discover possible preventive or ameliorative treatments. Further elaboration of the lesioning effects of kainic acid, including neurochemical sequelae of neuronal degeneration in the striatum, its effects on the disposition of neurotransmitters and their receptors, its influence on neuronal metabolism and ion permeability, and the characteristics of surviving dopaminergic terminals are in progress.

The discovery that GABA and its synthetic enzyme GAD were reduced in the brains of HD patients led to a number of different research questions. Scientists at Harvard Medical School are exploring the neuropharmacology of GABA function through the study of specific enzymes importantly involved in GABA metabolism. Investigators have developed highly potent and specific irreversible inactivators of GABA-transaminase (involved in degradation) and GAD (involved in synthesis). Gabaculine and derivatives inactivate GABA-transaminase and alpha-trifluoromethyl glutamate and alpha-methyl dehydroglutamate inactivate GAD. Scientists can thus regulate levels of GABA in tissue culture and in vivo. Using mice and chick embryos and tissue cultures, investigators will create models of HD and other disorders involving GABA metabolism, such as epilepsy. These models can be used to test potentially new treatments that would raise GABA levels. In tissue culture, the role of these two enzymes in the formation of gabanergic synapses and neuronal development can be studied in great detail. The investigators also propose to develop a new mapping technique for gabanergic neurons in culture and in vivo will be studied using radiolabeled decarboxylase inhibitors coupled with autoradiography.

Other animal models of abnormal movements are being studied at the Boston Children's Hospital Medical Center. A new mouse mutant which demonstrates unilateral turning with lesioning of the 5-HT pathways and appears to have an asymmetrical nigrostriatal system is being examined. Since the rats invariably recover with time, scientists are learning more about mechanisms of recovery from brain injury.

In the Fiscal Year 1979, the Neurological Disorders Program received 16 applications of which 7 were approved and 4 were funded totaling \$163,294 (direct costs only).

Alzheimer's Disease and Other Dementias of Aging

There was a time when the frailties and foibles of age were thought to be the almost inevitable price for witnessing the passing of years. With the impressive growth of tools, techniques, and hypotheses in neurobiological research, however, we are rethinking our future as well as uncovering the present. The devastating intellectual and physical decline, which is the hallmark of senile dementia, is seen now as a disease of aging; a pathological deviation from the normal developmental process. Clinical syndromes have been described, structural abnormalities identified, and the inner ocean of the cell penetrated.

The problem of the dementias in the United States is assuming alarming proportions. Projections from the National Center for Health Statistics indicate that by 1980 about 12% of our population will be 65 years or older. Based on northern European estimates of prevalence and incidence of dementia, there are approximately 1 million severely demented and another 3 million moderately to mildly demented persons in the U.S. today. The life expectancy of the severely demented is only one-third to one-half that of their age-matched controls, giving rise to an annual mortality rate of at least 100,000, conservatively calculated, and posing the alarming possibility that the severe senile dementias may be the fourth or fifth leading causes of death in America.

At least two-thirds of those with severe senile dementia suffer from Alzheimer's disease. In recent years, many scientists have argued that distinctions between these two disorders are arbitrary and meaningless. Although senile dementia of the Alzheimer's type (SDAT) and classic Alzheimer's disease, which usually affects people under the age of 65, may well be the same disorder, other forms of senile dementia with differing etiologies give rise to similar appalling symptoms. The spongiform encephalopathies, kuru and Creutzfeldt-Jakob disease, are the consequence of an unusual virus, or "viroid", which has properties unlike most conventional viruses. The span between infection and signs of the illness can be as long as 8 or 10 years. Once apparent, the diseases are characterized by vacuolation and neuronal death, astrocytic proliferation and hypertrophy, axonal and dendritic degeneration in Purkinje cells, and presence of amyloid plaques. Two cases of familial Alzheimer's disease have also been shown to transmit to primates to produce a clinical and neuropathological picture indistinguishable from Creutzfeldt-Jakob disease. Unlike Creutzfeldt-Jakob disease, transmission of Alzheimer's disease is the exception rather than the rule.

Occlusions of cerebral blood flow, known as multi-infarct dementia, also give rise to a clinical picture identical to that of SDAT. Sophisticated imaging devices, such as the CAT scan, help in making differential diagnoses.

Parkinson's disease dementia has received little attention, but it is a clinical entity of significance. Since the advent of L-dopa, improved motor control has thrown the cognitive changes in this disorder into bas relief. Parkinsonian dementia may be much more widespread than the special focus of patients on Guam who suffer from amyotrophic lateral sclerosis and

parkinsonian dementia. These patients, as well as other "usual" Parkinson's disease patients, show the neurofibrillary tangles so characteristic of Alzheimer's disease.

The NINCDS will take specific steps in the next few years to increase the level of research effort directed at elucidating the etiology and pathogenesis of these devastating illnesses. The Institute sees as its primary mandate to uncover and describe those factors which give rise to the disorders and which will lead to the development of new ameliorative treatments and preventive measures.

Structural and Biochemical Studies

The majority of the research supported is aimed at clarifying the structural and biochemical abnormalities which characterize Alzheimer's disease. A number of studies focus on the cytoskeletal changes, the neurofibrillary tangles and senile plaques, which are the hallmark of Alzheimer's disease. These tangles appear in the neuronal soma as aggregates of paired helical filaments approximately 200 Å in cross section, with a twist approximately 800 Å along their length. Both neurofibrillary tangles and their normal, unpaired, and nonhelical neurofilamentary counterparts have been identified as proteins with a molecular weight of around 50,000 daltons.

Other research sponsored by the Institute is characterizing the biochemical alterations in SDAT. A key feature in these changes are the neuritic or senile plaques, dense masses of extracellular amyloid surrounded by enlarged neurites, mostly axonal boutons containing degenerating mitochondria and lamellar lysosomes.

Investigators at Albert Einstein College of Medicine have had a long standing interest in elucidating the structural abnormalities and changes found in Alzheimer's disease brain tissue. One investigator is exploring the structure and function of the aging nervous system in humans and animals. Using organotypic cultures, he will study the effects of brain reactive serum antibody from old animals and people, including normal and demented individuals. Experimentally induced lipofuscin and aluminum induced tangles will be investigated as well as axoplasmic flow in aging animals. Another investigator is isolating and characterizing the intraneural paired helical filaments, mapping their peptides, binding properties, and antigenic determinants. A third scientist at Einstein is studying the biophysical properties of human and porcine neurotubule assembly and disassembly. Using proteins isolated from the autopsied brains of patients dying with Alzheimer's disease, both young and old, and Guam Parkinsonian dementia, the mechanisms of action of colchicine and vinblastine and the regulatory role of Ca, Mg, and Zn ions on microtubule assembly will be explored.

Understanding of the biology, chemistry and pathology of the fibrous proteins of the nervous system in health and in disease states has been the objective of many NINCDS supported researchers. Several different laboratories are investigating paired helical filaments in the presenile and senile dementias as well as in Down's syndrome. Twisted tubules have been partially purified by investigators at New York University Medical Center, and the relationships

among various neurofilaments described and between these filaments and tubulin is being explored. Another investigator at Boston Biomedical Research Institute is characterizing the chemistry and function of neurofilament proteins with regard to their sequencing, immunoreactivity, comparability with other glial fibrillary proteins, and tendency to proliferate in neurons treated by neurotoxic agents.

The role of the microtubules in maintaining cell integrity and function is exceedingly complex; explaining it may be necessary for understanding normative behavior as well as a variety of different disorders, including cancer and the dementias. In Colorado, investigators are looking at clonal cells of the mouse neuroblastoma C1300 that possess high concentrations of tubulin and whose content of microtubule can be directly regulated by growth conditions. The role of microtubule associated proteins in the initiation, elongation, and stabilization of microtubules during nerve cell differentiation will be explored as well as the possibility that these accessory proteins regulate where and when tubulin polymerization occurs with the cell. Work is also continuing on localizing and characterizing GTP binding sites in brain tubulin using photo-affinity labeling reagents.

Just as the structures within the cell have sparked interest, the structure which encloses the cell, that elaborate and vital membrane, has attracted the attention of others. Investigators at the University of South Carolina are asking if membrane transport alters with age. As the cell ages, can it still acquire across its membrane from the extracellular fluids the necessary metabolic substrates for energy metabolism and protein synthesis? Do membrane functions in neurotransmission remain the same? Scientists at the University of Missouri have preliminary evidence that some properties of mammalian brain membranes may change with age, and they are in the process of exploring their findings further. In addition to studying the structure, function, and active transport mechanisms of CNS membranes, the role of dietary antioxidants on membranes will be pursued.

When animals are given high doses of aluminum, they develop neurofibrillary tangles similar to those seen in Alzheimer's disease. An early report (since contested) claimed that Alzheimer's disease patients also had elevated aluminum levels in their brains. Although this finding is controversial, it did turn attention to the measurement of trace metals in brain tissue of Alzheimer's disease patients. Scientists at the University of Kentucky are looking at a wide spectrum of individuals, from birth to late life, with and without mental impairment, to determine levels of a wide variety of trace elements. In addition to the highly sophisticated and sensitive radiochemical neutron activation analysis being performed, the investigators have designed new instruments which do not shed metal into their preparations.

Genetics and Diagnosis

Genetic factors undoubtedly play a complex role in shaping the aging process, but we have much to learn about how they work their influence. Some cases of Alzheimer's disease clearly follow a Mendelian pattern of transmission (dominant) while in other families there seems to be an increased risk among relatives of a patient. If children with Down's syndrome (Trisomy 21)

live long enough, they often develop Alzheimer's disease.

Investigators at the University of Colorado have examined the chromosomes of members of families of Alzheimer's disease patients and have discovered greater aneuploidy than would be expected. They will follow these families to determine if aneuploidy may be a preclinical diagnostic sign as well as a possible etiologic clue.

Diagnosis of Alzheimer's disease is made on clinical grounds, more as a result of the elimination of other disorders than from specific signs. Confirmation must await autopsy. A recent NINCDS grantee is in the process of developing a rapid neuropsychological screening test which, hopefully, will be able to serve as an early screen for dementia. Development of the test will take place in a large, well defined retirement community in Southern California. Laboratory findings and other data will also be collected on this sample, making it an excellent prospective study for the identification of risk factors and possible etiologic clues.

Animal Models

Animal models of dementia are hard to come by since dementia involves the loss of a capacity we cannot be sure animals ever had. Nonetheless, scientists at the City of Hope in Duarte, California, are studying *Drosophila* mutants which exhibit both genetically programmed movement disorders and shortened life. They are trying to determine if the shortened life span is also under genetic control, and if so, how the genes produce their effect.

Another investigator at the University of Pennsylvania is looking at the aging process in cultured neurons. In the process, he is developing culturing techniques for neurons which may benefit research on many different brain disorders.

The NINCDS supported Neurological Center for the Study of Metabolic and Degenerative Disorders at Albert Einstein College of Medicine takes an interdisciplinary approach to studying inherited disturbances of metabolism, usually diseases of early life, and the dementias, most often striking the elderly. Clinicians, biochemists, neuropathologists and neurophysiologists, psychologists, mathematicians and many others turn their talents toward discovering the etiology of these diseases and developing appropriate treatments. Investigators have determined that, although neuronal loss is accelerated in aging, neuronal death is not a primary feature of Alzheimer's disease. Unlike the cells which die in Huntington's disease and Parkinson's disease patients, these neurons are altered but still present. This finding may have important implications for treatment.

Additionally, Center investigators have launched a prospective study in one of the local skilled nursing facilities and have been able to identify two distinct populations of patients, depending on age. The very aged (average age 85) suffer from multi-infarct dementia almost as much as from Alzheimer's disease.

The Institute is anticipating that research on the dementias will increase as the dimensions of the public health problems they spawn gain increased visibility. Research on Alzheimer's disease and related dementias remains a top Institute priority. The NINCDS is joining with the National Institute on Aging and the National Institute of Mental Health to develop new initiatives to increase research. One such initiative which has already taken place is the Second Workshop Conference on Alzheimer's Disease-Senile Dementia and Related Disorders. This Conference focused on the Clinical/Behavioral Issues in the Treatment of Alzheimer's Disease, Senile Dementia and Related Disorders, and was held in December, 1977.

In Fiscal Year 1979, the Neurological Disorders Program received 25 applications of which 17 were approved and 5 were funded totaling \$226,955, (direct costs only).

Related Disorders and General Studies

A disorder closely related to Huntington's disease in symptomatology appearing as a result of prolonged neuroleptic treatment is tardive dyskinesia. Unfortunately, no effective treatments have been developed for this disorder as well, but scientists at the Portland, Oregon, Veterans Administration Hospital are trying to determine a subgroup of this population which is responsive to therapy by deanol, a possible acetylcholine precursor.

The biochemical, structural, and functional characterization of the basal ganglia in general, unrelated to any specific disorder, has been drawing the attention of an increasing number of scientists. At the University of Texas, investigators are trying to understand the GABA receptor in all its complexity. The effects of drugs such as anionic transport inhibitors, anticonvulsants, and psychoactive agents are being explored as well as the possibility that altered chloride permeability may be a factor in disorders involving altered gabanergic function.

The pharmacological properties of intrinsic caudate neurons in cats are under investigation at the University of South Carolina, and at the University of Minnesota the organization and function of the cerebellum and spinal cord on motor control in monkeys is being studied. Scientists at Ohio State University are looking at the behavioral changes produced by amphetamines and related CNS stimulants and are determining the role of calcium as an enhancer of amphetamine effects. Scientists at St. Louis University have discovered an entire new group of tetrahydroisoquinoline alkaloids which can affect dopamine metabolism.

The wealth of research findings is steadily expanding, but so too are the numbers of victims afflicted by the disorders of aging. Increasing numbers of new investigators must be recruited to this area to maintain and accelerate the momentum of discovery.

In Fiscal Year 1979, the Neurological Disorders Program received 5 applications of which 5 were approved and 4 were funded totaling \$167,478 (direct costs only).

Convulsive and Related Paroxysmal Disorders

The epilepsies constitute the second most common neurological disorder in the United States involving approximately 1% of the population, about 2.4 million people. Many people with epilepsy live relatively normal lives largely due to successful seizure control using drugs. However, about 25% of the afflicted population have uncontrolled seizures. The frequency and intensity of seizures vary considerably. Mortality, either directly or indirectly due to epilepsies, has been identified in more than half of the cases; and half of these are attributed to suicide. An estimate is that life span is generally reduced as much as 10 years in persons with epilepsy.

Most laboratory research on epileptogenesis has been performed in animal models in which focal epilepsy has been produced because of the ease and reliability of the procedures. In fact, epilepsy may result from any form of brain trauma. For instance, injury during the perinatal or prenatal period may be causal. Head injuries, infection, congenital malformation, tumors, etc., may result in seizures at any point in life. Particularly discouraging to researchers is the fact that various forms of epilepsy can occur clinically without any evidence of morphological brain abnormality. Researchers have noted a high incidence of family involvement in epilepsy which may reflect genetically defective enzyme systems. Many incidences of seizures may be symptomatic of a variety of genetic diseases, each one having its own form of inheritance. Prescription and dosage of specific anticonvulsants tend to be determined experimentally. In a limited number of cases, where seizures appear intractable, surgical intervention has been indicated. In recent years the stress of accurate determination of serum drug levels has improved the efficacy of medication; in addition, these determinations have permitted the detection of toxicity, cross-reactions among drugs, and various metabolic difficulties. An important side effect of accurate serum drug level determination has been the detection of non adherence, absorption difficulties, and differences in drug metabolism among patients. Diagnosis has been assisted by the development of monitoring techniques using video recording and radio telemetry of the EEG simultaneously. Evaluation of the simultaneous EEG and clinical seizure has provided a more accurate determination of seizure type and a more reliable base for rapid evaluation of specific anticonvulsants and dosages.

During FY 1979 the NINCDS published a Request for Proposals for the synthesis of new potential anticonvulsant compounds. As a result of the RFA, 31 research grant applications were received, 17 approved and 11 funded. During the next three years the grant awardees will submit novel compounds for testing for anti-convulsive action by The Anticonvulsant Drug Development Program, Epilepsy Branch, of the Neurological Disorders Program.

During the period of this report 112 applications for research support in Convulsive and Related Paroxysmal Disorders were received; 65 were approved and 31 funded. Currently, there are 72 active grants in this category. These include six specialized research centers (epilepsy). The total amount of research support for all these activities is approximately

\$6,391,000. The grants are equally distributed amongst research in humans with the disease, the disease in animal models, and those processes believed to underlie various aspects of the disease. Researchers are particularly active in work on the pathogenesis of epilepsy and the mechanisms of action on anticonvulsant agents. The development of animal models for epilepsy continues with an interesting new possibility using autoimmune genesis for the disorder. This new model has promise as a model for generalized seizures as opposed to the focal seizures produced using cobalt, aluminum, or other specific agent. Work continues on the neurophysiological, morphological, and biochemical abnormalities that may underlie focal epileptogenesis. Intracellular labeling techniques are particularly popular for studying this problem. Some work, using hippocampal slices, suggests that some forms of epileptiform discharge may be intrinsic to nerve cells rather than due to large synaptic potentials. Various neurotransmitter substances are being studied to determine their roles in seizure genesis and termination. Other research continues on the trauma produced by epileptic seizures themselves. The disease is considered to be progressive by many workers in the field. Mechanisms of action of various anticonvulsant compounds are being studied using identified single neurons of invertebrate preparations.

Studies of patients with generalized epilepsy and generalized spike-and-wave discharges show that ethosuximide produces an attenuation in the number and duration of spike-and-wave discharges; this attenuation may progress with increasing doses to abolition of the activity. At a critical point in this process, absence, atonic, and myoclonic seizures cease, but generalized tonic-clonic seizures may occur as long as some spike-and-wave activity persists.

Additional studies have been undertaken this past year with reference to the anti-epileptic drug valproic acid, (VPA) in the treatment of epilepsy. Because VPA is highly bound to plasma protein, several variables affecting such binding significantly alter the quantity of free drug which is pharmacologically active. Studies in vitro with equilibrium dialysis and ultrafiltration studies of VPA binding of plasma protein have been accomplished, and a clinically significant alteration was found in the percentage of free VPA when the total drug concentration exceeded 80 micrograms/ml. Human plasma which is low in albumin was found to have twice the quantity of free VPA as normal plasma. Also, the clinical evidence of interaction between VPA and phenytoin is confirmed by the increase in the free fraction of both drugs. The approach to the clinical evaluation of valproic acid was altered this past year when the drug was approved by the FDA for general use in the treatment of seizures. Investigators have continued to follow 22 patients started in open trial in 1975. No side effects of significance have appeared. It was found that VPA was not of particular benefit in the treatment of patients with numerous partial complex seizures. Only one of an original group of 18 patients with such seizures continued to show complete control after three years. However, VPA has been found to be quite effective in the control of absence seizures, including effects of subclinical seizure activity as shown in the , electroencephalogram. There have been significant effects in the control of major tonic-clonic seizures.

A clinical investigation of epilepsy and the menstrual cycle is in the final phases. The principal hypothesis is that progesterone inhibits seizures, and consequently women should have fewer seizures during the mid-luteal phase of the menstrual cycle when progesterone levels are highest, and seizure frequency should be greatest menstrually and premenstrually when progesterone levels are rapidly falling. The results to date indicate that in about 75% of the epileptic women studied, seizures do cluster during the menstrual and premenstrual phases of their cycles. Seizure activity is least great both when progesterone levels are high in the mid-luteal phase, but also in the late follicular phase just prior to ovulation. Various psychological tests indicate that subjects perceived life stresses more intensely, menstrually and pre-menstrually; stress occurring during other phases of the menstrual cycle was related to increased seizure frequency as well. Higher anxiety levels were measured during the menstrual and premenstrual phases of the cycle, as well as indications of increased tension, depression, anger and fatigue.

Work on mechanisms of action of convulsant and anti-convulsant agents continued. Certain investigations have dealt with pharmacological interactions between the drugs and potassium conductances. The relationship of their responses to calcium activities pointed to a different mechanism of action for different drugs. The effect of an interesting alkaloid, Sparteine, was studied since it was known to produce convulsions in laboratory animals. The sensitivity of neurons to the drug coincided with their ability to sustain active membrane responses dependent on calcium, strontium and sodium-free solutions, and further supported the theory that the differential sensitivity of a drug could be accounted for by the amount of calcium it can admit during depolarization.

Previous studies in one laboratory have demonstrated that phenytoin inhibits calcium-dependent phosphorylation of particular brain proteins at therapeutic concentrations of the drug. The drug also was found to block several calcium-dependent release processes, and the hypothesis was developed suggesting that antagonistic actions of calcium and phenytoin on the level of phosphorylation of proteins may be a major basic molecular mechanism mediating the drug action of the release of neurotransmitter from the presynaptic nerve terminal. These effects were shown to be present in synaptosomes, and during this past year a more physiologically active synaptosome or synaptic vesicle preparation was developed. It was found that neurotransmitter, norepinephrine, content of the vesicles was significantly influenced by methods of preparation. Calcium ions were found to cause a marked decrease in the norepinephrine content of these highly enriched vesicles and an increase in the amount released. The action of calcium was dependent on the presence of magnesium.

Other recent investigations show that in mouse brain slices, phenytoin inhibited elevations of cyclic GMP and cyclic AMP produced by ouabain or veratridine. In contrast, elevations of the two cyclic nucleotides, produced by high concentrations of potassium were not inhibited by phenytoin, suggesting that the anticonvulsant suppresses depolarization-induced elevation of cyclic nucleotide levels in brain slices by inhibiting influx of sodium

into cells. These data suggest that phenytoin inhibits both sodium and calcium influx into cells during cellular depolarization and alters regulation of brain cyclic nucleotide levels. Both of these actions may be important for the antiepileptic effect of phenytoin.

Levels of cyclic AMP and cyclic GMP were measured in cerebral cortex, cerebellum, striatum, thalamus, and hippocampus of mice prior to and during seizures induced by pentylenetetrazol. The data indicate that seizure activity affects cyclic AMP and cyclic GMP differently in various regions of the CNS nucleotide levels are dependent upon the type of seizure activity. The results also suggest that not all of the changes in levels of cyclic GMP produced by pentylenetetrazol are a consequence of seizure activity, but that those of cyclic AMP are.

VPA was applied to Aplysia neurons and found to cause a specific increase in potassium conductance with an associated hyperpolarization of the resting membrane potential. VPA also was found to decrease the duration of excitatory post synaptic potentials (EPSP's) and reduce spontaneous bursting.

One series of experiments dealt with the basic mechanisms of normal neuronal activities and the alterations produced in them during epileptogenesis. Results to date have furnished new information about the functions of mammalian cortical dendrites, and the mechanisms of normal and epileptogenic burst generation. Data show that burst generation is intrinsic in CA3 cells of the hippocampal slice. Spontaneous bursts contain low threshold sodium and high threshold calcium spikes. The depolarizing envelope of the burst appears to be a summation of spike depolarizing afterpotentials and longer-time-course depolarizations. Since previous experiments suggested that dendritic spike generation was involved in dendritic spike (DS) generation, investigators studied both the normal behavior of hippocampal pyramidal cell dendrites and the effects of penicillin on the activities of dendrites in the CA1 region. Electrophysiological properties of dendrites were significantly different from those of the somata of CA1 neurons in that direct depolarization evoked bursts at low threshold in dendrites, but not in cell bodies. By contrast, in CA3 pyramidal neuron bursts could be directly evoked in somata and dendrites. Differences in burst structure were present in dendrites versus somata which allowed electrophysiological identification of the recording site. Simultaneous impalements of dendrites and some of single CA3 neurons showed that dendritic bursts could trigger somatic ones, and vice versa. After penicillin application, orthodromic stimuli, which had previously elicited excitatory post synaptic potentials - inhibitory post synaptic potentials (EPSP-IPSP) sequences in CA1 cell dendrites became effective in evoking epileptiform field potentials and dendritic bursts. This change coincided with the apparent depression of a dendritically recorded IPSP and prolongation of the EPSP. EPSP amplitude was unaffected. These and other data indicate that penicillin gives rise to DS generation in CA1 neurons by blocking inhibitory control of intrinsic burst generation in dendrites. In ongoing experiments these investigators are examining the hypothesis that DS generation induced by penicillin in neocortical neurons is intrinsic to the involved cells, rather than the result of summed "giant" synaptic potentials.

Measurement of baseline $[K^+]_o$ and $[Ca^{++}]_o$ and alterations in the distribution and concentrations of these ions were made in hippocampal slices maintained in vitro under normal conditions and during pencillin-induced epileptogenesis, using ion sensitive microelectrodes (ISMS). Orthodromic stimulation (stratum radiatum) produced increased $[K^+]_o$ and decreased $[Ca^{++}]_o$ which were maximal in the stratum pyramidale and decreased $[K^+]_o$ in stratum oriens. Stimulation of pencillin-perfused slices evoked burst discharges and larger ionic shifts. Intracellular recordings have been obtained from glial cells in the hippocampal slice which show that their activities are very similar to those of glial cells in vivo. It has already been possible to label glial cells with HRP and to record from them simultaneously with recordings from potassium ISMS located extracellularly. These experiments provide additional evidence that substantial non-synaptic modulation of excitability may occur in cortical neurons as a result of extracellular ionic shifts during stimulation and epileptogenesis.

Other researchers hope to develop a reliable model of chronic epileptogenesis in animals in order to study functional alterations in the involved elements. They are using ferric chloride to make chronic epileptogenic foci in neocortex and hippocampus of rat, cat, and guinea pig. Successful pilot recordings have been obtained from hippocampal slices from some animals. Preliminary findings are that CA1 neurons of injected hippocampus generate burst discharges with orthodromic activation.

A study of CA1 cell behavior following exposure to pencillin or bicuculline has been completed. Results show that burst discharges typical of epileptogenesis result from depolarization shifts which are non-synaptic in nature. The data are consistent with the hypothesis that IPSPs prevent orthodromic activation from eliciting intrinsic burst discharges in these cells. Significant burst responses originate in dendrites.

The main purpose of another project is to determine whether local, asymptomatic, interictal epileptiform discharges in neonatal animals can affect the developing nervous system. These investigators create local epileptiform discharges in newborn rabbit starting from 8 days and lasting 27 days of age. They find that projected paroxysmal discharges affected normal development of lateral geniculate neurons. These detrimental effects had an initial critical period not demonstrable in adult rabbits. They also recorded cortical neurons adjacent to the discharging EEG focus in the opposite striate cortex to determine if such interictal spikes also affect the development of striatal neurons. The results clearly show that there is an abnormal development of neuronal types in the striate cortex adjacent to the epileptogenic focus.

Other investigators have used the isolated-hemisphere preparation in the cat to investigate the role of thalamocortical mechanisms in the elaboration of generalized epilepsy. Their observations suggest that an intact thalamocortical system is necessary for the production of paroxysmal spike-and-wave activity in generalized pencillin epilepsy. Epileptiform activity was induced in the chronically isolated hemisphere, demonstrating that penicillin was reaching the cortex and exerting a primary convulsant action on cortical structures, in the absence of subcortical connection.

However, the character of the epileptiform discharges in the isolated hemisphere differed considerably from that of the intact side. The important observation was that spike-and-wave paroxysms did not occur in the completely isolated hemisphere following penicillin administration. These results support the view that the basic pathophysiology of generalized penicillin epilepsy, and theoretically of analogous spike-and-wave activity in petit mal epilepsy, consists of a diffuse cortical epileptogenic state, with full elaboration of the generalized, bilaterally synchronous discharges dependent on the presence of subcortical structures.

Apparently epileptogenic foci such as those produced by topical application of penicillin to the cortex exert excitatory effects on neurons in distant, anatomically related, structures - e.g., contralateral hemisphere and dorsal-column nuclei - and can antidromically activate neurons whose axon terminals project into a focus. An important consequence is that excitability in the primary focus may be modified subsequent to projected activity, because many of the structures receiving projected epileptiform discharges are known to be reciprocally connected to the site of discharge origination.

In a study of the effect of phenobarbital on Aplysia burst-firing neurons, it was found that low concentrations enhance inward calcium conductances, particularly the slow calcium conductance that mediates burst-firing. At higher concentrations, however, phenobarbital has an opposite effect - decreasing inward calcium conductances and burst-firing. It was also found that neurons that possess slow inward calcium conductances, but are silent under normal conditions, can be transformed into spontaneously bursting neurons with a slight increase in extracellular potassium.

Other investigators are trying to identify the antigenic sites in synaptic junctions whose combination with specific antibodies will induce seizure activity, to determine which regions of brain are susceptible to such insult, and to establish the mechanism underlying the induction of the seizures. Ten antisera have been tested for their effectiveness in producing recurrent epileptiform seizures following intracortical injection. Five of these antisera were effective, giving positive effects in 41 of the 45 animals tested. The immunoneurological model of epilepsy has several advantages over other models, one of the most important being the potential for specific localization of antigen sites on cells or in synaptic junctions that may be responsible for seizure activity. Since immunological methods provide specific molecular assignments for reaction sites, it is possible to determine whether one or many different antigenic receptors in synaptic connections may be involved. The immunological damage to brain tissue is minimal in this model; this is close in character to clinical epilepsies of non-traumatic origin. Studies of a well-defined, readily available antigen-antibody system should serve to make this model available for a broad spectrum of investigations in the area of synaptic pathology induced by antibodies.

There is some research activity in the use and understanding of behavioral interventions for seizure control. It has been determined in one laboratory that a systematic long-term modification of EEG activity by

electronic feedback training is possible. A detailed protocol was developed, utilizing mainly a single blind crossover design with specific attention to placebo possibilities. Epileptic persons were trained to increase low voltage fast EEG activity which simultaneously reduced high voltage slower wave activity. This investigation, thus far, has demonstrated significant reduction in seizures in 3 of 5 patients. These patients all had either focal motor or partial complex seizures. The decrease in seizures was in the range of 60%, comparable to the 65% average reduction reported by other investigators. This could not be correlated with changes in medication or AED blood levels. Changes in the EEG associated with seizure reduction were toward "normalization." It was also found that the decrease in seizure activity as a response once "learned" by the technique, did not extinguish rapidly in the patients where this had occurred. The results have shown that clinically significant reductions in epileptic seizure activity can occur in certain patients with EEG feedback training.

Since the beginning of another project, 18 drug-refractory or poorly controlled seizure disorder patients have been studied under various experimental paradigms in the application of central cortical EEG operant conditioning. Clinically, these patients have represented a rather diverse group since poorly controlled patients often manifest mixed seizure types. Moreover, many of these patients have long seizure histories with continually changing drug treatments. An overall mean seizure rate reduction of 65% was reported during the period of direct participation in these studies ranging from 1-3 years. These gains were sustained in all patients for periods ranging from 1-7 years. Five patients reported a complete cessation of major motor seizures during and following participation in these studies. One of these patients has been seizure-free for four years. Four patients reported no consistent change in seizure rate throughout the period of study.

The most effective approach for training is emerging: "normalizing" the EEG by suppressing epileptiform discharges and by enhancing "normal" EEG activity. This hypothesis is being tested in several behavioral science laboratories.

One investigator has developed an animal model that may explain the efficacy of biofeedback training. In studies of focal epilepsy produced in the rhesus monkey by aluminum cream injections into sensorimotor cortex, he reported a reduction in abnormal cellular discharge patterns with operant conditioning of unit firing rates. Epileptic animals trained to either increase or decrease cellular firing rates showed a gradual reduction in the number of abnormal cells encountered in and around the experimental focus. Concomitant with this change in neuronal behavior was a decrease in the number of documented seizures. The investigator has proposed several explanations for these effects, one of which invokes a reduction in abnormal synaptic excitability as a result of induced neuronal changes.

An investigative team is developing an electronic means for identifying electrical activity of the brain that predicts seizures. The objective is to enable persons with epilepsy to know in advance that a seizure is forthcoming and to take appropriate action. Thus far, work on the development of methods to predict the occurrence of spike-wave bursts has yielded consistent results. Replicable, although individually distinctive, changes

have been seen using power spectral frequency analysis and comparison of pre-burst and control segments. The methods of analysis have been refined, and satisfactory and reliable work algorithms have been developed for the PDP 11/40 computer. Thus, the work is progressing. Overall, research in the convulsive disorders has progressed during 1979 and the implications are that it will continue to do so during 1980.

Demyelinating and Sclerosing Disorders

The demyelinating and sclerosing disorders sub-program supports research devoted to elucidation of the etiology and pathogenesis of Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS).

As a consequence of Congressional interest, the Report and Recommendations of the National Commission on Multiple Sclerosis was issued in 1974. Thereafter, the Neurological Disorders Program of the National Institute of Neurological and Communicative Disorders and Stroke organized a "Work Group" to consider the MS Commission's recommendations. An appropriate balance of priorities had to be determined, maintained, and implemented by the Institute Director, Program Director, and their staff. The majority of the MS Commission recommendations have been implemented.

In the fiscal year 1978, 68 grants were awarded (including six MS, one ALS, and one ALS-MS clinical research center). Total cost expenditures in support of these activities was \$7,889,436. A total of 76 applications were received in FY '78 of which 16 new and 15 competing renewals were funded with an expenditure of \$1,208,432 for new and \$1,368,573 for renewal grants. As of July 1, 1979 this program supports 77 research projects with a total cost investment of over 9 million dollars.

Multiple sclerosis (MS) is one of the most common chronic neurologic diseases in the United States today. More than 250,000 patients are crippled by MS. This disease characteristically afflicts young adults and consequently, the burden on both the individuals and families involved is multiplied in the societal losses.

In MS a destructive process of demyelination takes place. Myelin, the protective sheath normally present around most nerve fibers is destroyed or dissolved. This process is usually followed by a reaction of non-neuronal nervous tissue (astroglia) which leads to scar formation and hardening. Further, areas of demyelination are scattered in the brain and spinal cord which lead to such symptoms as double vision, inability to maintain balance, numbness, or paralysis of parts of the body, tremor, nystagmus, speech and elimination difficulties. Demyelination is a primary effect, occurring at random, and is associated usually with a lesser deterioration of the nerve fiber itself.

The cause of MS is not known and there is no effective long-term treatment. Since Charcot originally described MS more than 100 years ago, neurologists and neuropathologists have noted an expanded spectrum of clinical and pathologic variation from individual to individual afflicted with MS. In the 1950s, epidemiologic studies indicated both high and low-risk prevalence areas for MS. Further studies on migrant populations suggested that MS was acquired in childhood although clinical disease is not manifested until adult life. While these data were accumulating, the concept of the "slow-virus" neurologic disease was developing, with apparent incubation periods of many months or

years. The concept that MS might possibly be a viral disease with a long incubation period was an attractive hypothesis supported by the blending of fruitful MS epidemiologic studies with the knowledge that the spongiform encephalopathies (including human Creutzfeldt-Jakob) were transmissible and also that other chronic neurologic disease of man such as subacute sclerosing panencephalitis (SSPE) and progressive-focal leukoencephalopathy (PML) were directly associated with virus infections.

It is presumed that the viral agent or agents established a latent infection which periodically becomes activated leading to myelin destruction. Whether this is the direct effect of the virus or a non-beneficial immunologic reaction possibly provoked by a secondary viral infection or a nonspecific inflammatory response is not known. The relationship between a viral infection and subsequent alteration of the immune system has begun to be studied in recent years. Little is known about the ability of virus to infect and produce disease of the oligodendrocyte (the cell responsible for the production of myelin). Furthermore, the factors in the sera of patients with MS which can demyelinate myelinated cultures in vitro are not well characterized. The extent to which remyelination occurs in MS and the role of immunologic or other factors which might inhibit remyelination are are unknown.

Since the major CNS elements damaged in MS are the myelin sheaths, the membranous insulation of nerve fibers, and their supporting cells, oligodendrocytes, and since epidemiologic studies indicate that the disease is acquired sometime before adolescence, most etiologic and pathologic considerations implicate an abnormal immunologic response to CNS elements and/or a persistent infection by a defective virus.

The neuropathologic research supported at Albert Einstein College of Medicine has been interdisciplinary and largely directed towards the elucidation of immunopathologic events implicated in the pathogenesis of the demyelinated lesion in MS. Foremost in recent achievements has been the continued development and successful application of their model of chronic relapsing experimental allergic encephalomyelitis (EAE). This condition, inducible in inbred Strain 13 guinea pigs with a single inoculation of CNS tissue, possesses striking clinical and pathologic similarities to the human disease. During the current grant period, the investigators explored the feasibility of monitoring the clinical, structural and immunologic (lymphocyte population dynamics) parameters in this animal model during the relapsing course and have related the findings to the situation in MS. This work revealed that these parameters fluctuate with disease activity in a manner reminiscent of MS. Furthermore, in view of an increasing interest in myelin basic protein (MBP) therapy in MS, they found that MBP successfully prevented the development of this chronic disease and that this suppression might be related to concomitant increases in certain subsets of circulating lymphocytes. Surprisingly, it was also shown that the suppression was permanent since a second challenge of suppressed EAE animals with the nervous tissue antigen failed to elicit disease onset. Also, CNS repair

was enhanced in suppressed animals. On the other hand, unsuppressed guinea pigs developed new disease after a second challenge. With the initial onset of signs in EAE, it was observed that a population of circulating lymphocytes decreased significantly. By a subsequent novel experiment, they showed that this dramatic decrease in circulating T-lymphocytes was matched by the appearance of similar T cells within the CNS, suggestive of lymphocyte migration to the target organ. Of significance to the MS situation is the possibility that MBP administration to chronic EAE animals prevents or alters the migration of such cells to the CNS and at the same time causes the generation of a population of cells with suppressor activity within the circulation. The application of this combined clinical, pathologic, and immunologic approach of chronic EAE represents one major advance in the understanding of immunopathogenetic events in MS.

Other achievements in this laboratory have included: a) the production and characterization of a specific antiserum to the cell which produces and maintains central myelin, the oligodendrocyte -- to be used in future immunocytochemical studies on the behavior of this cell type during demyelination; b) investigation of the possible role of an anti-oligodendrocyte antibody in the course of MS by a series of carefully controlled experiments which showed that serum factors to oligodendrocytes in the serum of MS subjects are not specific to MS, do not represent specific antibody, and do not correlate with disease activity; c) experiments using cultures of living CNS and PNS tissue exposed to demyelinating antiserum from animals sensitized against whole CNS or PNS tissue. This approach has been followed for many years in this laboratory in collaboration with others, and permits the investigator to observe the effects of selected factors, e.g. serum, in the absence of a host immune system. Recent findings have shown that complement-depleted (heated) anti-CNS or anti-PNS serum will cause a unique proliferation of CNS or PNS myelin (respectively) in vitro. This is evidenced by the apparent stimulation of the myelinating cells to proliferate copious amounts of redundant myelin which has a unique ultrastructure. Ongoing work along these lines will attempt to characterize the serum factor(s) responsible for this unusual behavior of the myelinating cell; and finally, d) experiments conducted to localize and characterize immunoglobulins and viral antigens within the CNS of MS subjects. While this approach provides one promising avenue by which to demonstrate its presence, specific factors in MS have not yet been found.

Since MS appears to be a uniquely human disease, every possible effort must be made to study the disease in man. This requires the ready availability of patients with MS and the interaction of a group of investigators capable of multidisciplinary approaches. In such a collaborative program, tissue becomes available for examination when appropriate. Blood, cerebrospinal fluid, and autopsy specimens can be examined immediately and do not have to be preserved by procedures which could lead to irreparable damage of a potential MS agent, and immediate availability makes possible studies of cell-mediated immunity. Therefore, extensive programs are built on our present knowledge using

newer virologic, immunologic, and central nervous system culture techniques. An example of the power of the studies which become possible in man is the potential for immunologic studies of cells from cerebrospinal fluid of patients with MS as the result of increasingly miniaturized, sophisticated techniques.

However, parallel and more wide ranging studies must be carried out in animal models which permit us to address such questions as the neuro-tropism and potential for damage to the oligodendrocyte or myelin by viruses, the immunologic response to viral infection, studies of immune compartmentalization which require analysis of brain tissue, and studies of the immunogenicity of myelin lipids. Techniques and knowledge which arise from these studies can be applied to studies performed with human material. Consequently, a strong effort is organized around these research themes between members of the groups at the University of Pennsylvania and the Wistar Institute and similar approaches are taken at several other MS clinical research centers.

Numerous physiologically or pathologically active molecules such as certain hormones (insulin), growth factors (Epidermal Growth Factor, Nerve Growth Factor), neurotransmitters, toxins (diphtheria toxin, cholera toxin, tetanus toxin), lectins, etc. bind with high affinity to specific plasma membrane receptors. The mechanism of action of these molecules is not yet understood but it is reasonable to assume that the initial binding of a molecule and its receptor, the subsequent redistribution in the plane of the plasma membrane of molecule-receptor complexes, and the uptake (endocytosis) by the cell of the molecule-receptor complexes are linked with the initiation, propagation, and possibly with the termination of the physiologic or pathologic effect.

Investigators at the University of Pennsylvania have focused on the endocytosis of various molecules (antiimmunoglobulin antibodies, lectins, cholera toxin) which bind to corresponding plasma membrane receptors of lymphoid cells or neurons. They found that these molecules undergo endocytosis in the general area of the Golgi apparatus and specifically in a system of vesicles and cisternae which are positive for acid phosphatase, the so-called GERL (Golgi-Endoplasmic Reticulum-Lysosome). The functional implications of this unusual pathway of endocytosis are being studied. They believe that this pathway might serve either the recycling and re-utilization of receptors or the special degradation of plasma membrane moieties. They are conducting experiments which will clarify the role of endocytosis of receptor ligand complexes in initiating the cell response to a toxic molecule (ricin) or to a toxin which mimics hormonal actions (cholera toxin).

They believe that these studies on the dynamics of plasma membrane are basic to many problems of human neuropathology. Neurons and glial cells are characterized by an extraordinary high ratio of cell surface to cell volume. Cells' surfaces must play a key role in physiologic and pathologic processes. Diseases such as human or experimental myasthenia gravis, diabetes mellitus, or the various forms of receptor deficiencies of low

density lipoproteins (LDL), serve as examples of the relevance of cell surfaces in general and of receptors specifically, in pathologic processes.

Allergic encephalitis, especially experimental allergic encephalomyelitis (EAE), attracted the attention of scientists for several reasons. It can be induced in a laboratory animal by injection of nervous tissue or BP (basic protein), a component of myelin. This model is a promising experimental model to study MS and other demyelinating diseases of man. While it is not the perfect animal model of human MS, it is highly relevant to the fundamental research in the demyelinating diseases.

For example, research at the Wayne State University is focused primarily on the mechanism governing immunologic tolerance to EAE. Normally, the body does not respond immunologically to autologous antigens, a phenomenon known as "self-tolerance." However, EAE is an exception, since the host can be induced to respond to MBP which is a self-antigen present in the myelin sheath of the central nervous system (CNS). By immunizing animals with BP in Freund's adjuvant (which enhances the immune response), self-tolerance can be readily broken down. As a result, the immunized animal produces self-reactive T-lymphocytes which are specific for BP. Since BP is a major protein component of myelin, these lymphocytes (effector cells) bind to and destroy myelin in the CNS, and the animal becomes paralyzed.

Since self-reactive lymphocytic effector cells can be induced by appropriate immunization, it seems clear that self-tolerance cannot be simply defined as an inability to react against autologous antigens. The implication, therefore, is that a regulatory mechanism controls immunologic self-reactivity. The immunoregulation of EAE in inbred Lewis rats has been the thrust of this group's recent research activity.

They have found that suppressor cells regulate EAE and have determined the requirements for the induction of these cells. Suppressor cells are induced by injecting rats with BP in a nonimmunogenic form (i.e., without adjuvant; EAE is not produced). The suppressor cells localize in lymph nodes and spleen and have been identified as a subpopulation of T-lymphocytes, although there is some evidence that macrophages may also function as suppressor cells. The suppressor T-lymphocytes appear to prevent the induction of disease-inducing effector cells in this model system.

One implication of this finding is that the functional inactivation of suppressor cells may lead to the appearance of effector cells which in turn cause demyelination. This could explain the phenomenon of human demyelinating diseases.

A finding of considerable potential importance has resulted from the collaborative effort between Duke University Medical Center and the Northwestern University Medical and Dental School. Because of their

special expertise in immunochemistry and radioimmunoassay developed in the area of myelin immunology under earlier grant support, an attempt was made to answer the question of why baby rats are unusually resistant to the induction of EAE. Could it be that this display of tolerance was due to the presence of the antigen, MBP, in the circulation of these rats that dampened their immunologic response to injections of the antigen? The team at Duke University looked for immunochemical evidence that this was so in samples sent to them under code from Northwestern University. They found some samples with MBP in them, others without. When the code was broken, the MBP-positive samples were from the suckling rats, the MBP-negative ones from adults.

However, with increased sensitivity of the method, they found definite evidence of serum MBP at very low levels in the adult. Pursuing the analysis still further, they began accumulating indirect evidence that the serum MBP was not the intact form of the protein as it exists in the myelin sheath, but in the form of circulating fragments. Sometimes one fragment would appear, sometimes another; infrequently all fragments were present. Currently they are isolating and purifying some of these fragments in order to have direct evidence for their existence and hopefully to pinpoint their place in the MBP molecule. The difficulties they face stem from the extremely small concentrations involved: the amount of MBP fragment in adult blood, for example, may be so small that it would take 50 gallons to yield the equivalent of a 5-grain aspirin tablet.

What does all of this mean with respect to human CNS disease? In Atlanta in the 1978 J. E. Smedel Lecture the following was concluded, "... the impressive degree of concordance of immunologic events in EAE, ..., and MS provides ... support for the central importance of host neuroimmunologic responses in the pathogenesis of these neurologic diseases." The speaker pointed out that "circulating MBP or MBP fragments may be of great importance in inhibiting neuroautoimmune reactivity and play a role in repair of immunologic CNS injury should it inadvertently occur."

Thus, what began under the aegis of an NINCDS grant as an immunochemical analysis of myelin architecture some seven years ago has become an immunochemical search for myelin fragments in the circulation. Consequently, the assumption now is that some of the major events that determine whether "neuroautoimmune reactivity" spills over into the brain itself take place in blood.

An investigator at University of Maryland deals with the problems of how myelin membranes (layers of cell membranes which wrap around the axon of the neuron) are destroyed by immune mechanisms operative in diseases like MS. Specifically, he wants to know how humoral immune factors such as antimyelin antibodies and complement can damage the myelin. The complement system (14 proteins present in blood and body fluids) is known to damage the lipid layers of cell membrane when they are "activated" by antigen-antibody complexes or by various microorganisms. Experiments

are being designed to determine whether these "membrane-attack" complement systems can insert their peptides into the myelin membrane when they are "activated" by anti-myelin antibodies, thus creating transmembrane pores or how they destroy the membrane by removing lipid from the membrane. It is also possible that both mechanisms may work together.

The second part of this research is concerned with the modulation of myelin membrane lipid. The information obtained in studies of myelin membrane damaged by the complement system could contribute directly to the membrane modification studies. The investigator has already done a considerable amount of work in this field with sheep erythrocyte membrane and with liposomes (artificial membranes made with known chemical components of lipid). Through these experiments, we have learned that certain unsaturated lipid is more susceptible than their saturated lipid counterpart, and lipid with longer chain length behaves like the saturated lipid when they are attacked by complement. Furthermore, cholesterol in the membrane protects and reduces the extent of damage.

Research is now exploring ways of modulating the myelin lipid composition to learn what types of chemical or physical changes in the membrane can reduce the extent of myelin damage under these circumstances. It is well known that the nature of lipid in diet can directly influence the chemical composition of cell membrane lipid. In this way, they can affect the effector phases of demyelinating diseases possibly through diet since understanding and preventing the initiating phases of these diseases are far more remote goals.

The third aspect of this proposal deals with a practical problem, namely, how can we quantitatively detect antimyelin antibodies present in patients' serum or cerebrospinal fluid (CSF)? The only method now available involves newborn mouse central nervous tissue explant culture. It requires large quantities of patients' CSF or serum to observe myelin destruction in this system. The culture technique is difficult; it takes about a month and the results are not quantitative. Therefore, they would like to develop assay techniques with liposomes made with extracted myelin lipid. The extent of trapped markers released from the liposomes when they are treated with antimyelin antibody and complement should reflect the titer of antibody present in test sample.

The current thrust of the MS research activities is understanding the etiology of demyelination. The grants support studies of brain autopsy, or biopsy of pathological material, which is used for cell isolation, and biochemical, physiological, immunological, and histochemical analyses. These studies are a part of wider investigations, such as research on the biochemistry of normal myelin, membrane biophysics, and pathological processes in animal models. For example, an immunoenzymological approach is being used to develop indicators of myelin development and possibly also of the demyelination. Growth characteristics of cells isolated from PNS and CNS are being studied in vitro. The effect of macrophage secreted proteases on myelin degradation are investigated as one possible mechanism of demyelination. Comparative X-ray diffraction studies of mature,

immature, and abnormal myelins derived from various species are being carried out. Nuclear magnetic resonance (NMR) spectroscopy is being used to study interactions between MBP and myelin specific lipids. New techniques and instrumentation are being developed to study membrane structure and membrane models. The demyelinating effect of serum from MS patients and EAE is being analyzed.

Recently developed oligoclonal immunoglobulin assay can confirm MS diagnosis in about 85 percent of cases. However, there is great interest in developing even better and more reliable tests for MS. A highly sensitive radioimmunoassay is being used to assess demyelination and myelination process on nucleotide rich material (NRM), which is unique to MS found in the spinal fluid. Further, an attempt is being made to verify the presence of neuroelectric blocking factor(s) found in serum obtained from patients with MS.

It was found that the CSF from MS patients has myelinotoxic effect; therefore, further studies are being conducted to assess its diagnostic potential for MS. Parameters of neuronal and cell-mediated altered immune responsiveness are correlated with the clinical course of MS patients in an attempt to develop a more specific diagnostic test for MS. Idiotypic antibodies are being determined in CSF of patient as markers of MS. An attempt is being made to standardize solid phase radioimmunoassay for brain phospholipid protein (PLP) measurement at various stages of MS.

Although the medical profession is not yet able to treat MS directly, the medical management presently used may protect patients from exacerbations, recurrent infections, and may ameliorate symptoms. The treatment in some instances arrests the disease's progress, but in general it appears to be symptomatic. It was found that the steroid therapy in combination with cyclophosphamide prolongs remissions, and large doses of adrenocorticosteroids have a positive effect on the clinical course and may be helpful in the treatment of acute exacerbations of MS.

ACTH has been utilized with debatable results for treatment of MS patients. A current study is attempting to assess the value of L-tryptophan and electric stimulation for improvement of certain signs and symptoms occurring throughout the course of MS. Another study is exploring immuno-suppressive therapy with azathioprine, and prednisone with azathioprine which after a period of time may become ineffective in the treatment of chronic MS. The immunopotentiating agent, Levamisole, has been investigated. Also of great importance is the management of the patient's emotional status. Tension, frustration, and depression have and depression have an effect on the endocrine system which plays a yet unexplained role in the disease.

The Institute support of research in endocrinology is moderate. It involves research in hormonal regulation and control mechanisms, hormone binding, hormone receptors, hormone analogs, biosynthesis, inhibitors, and metabolism, peptides, neurotransmitters, and immunoglobulins. However,

hormonal studies of MS patients are very limited. Our Institute's financial support data indicates little activity in this area of research in the U. S. Because the currently favored hypothesis is for the viral etiology of MS, a major interest and research effort has been directed toward this area. There is now, however, considerable evidence to support the view that MS is an autoimmune disease. Consequently, we can expect an increased research effort in the area of hormonal regulation of the immune response.

Investigations at the University of California at Los Angeles during the last year have expanded knowledge of environmental, familial-genetic, and immunologic factors associated with the pathogenesis of MS. Studies of the prevalence of MS among American-born migrants to Los Angeles and Seattle from low and high prevalence areas within the United States have suggested that the risk of MS increases with the age at migration up to at least age 20. This effect was observed regardless of the area from which these individuals had migrated and whether they migrated to either Los Angeles or Seattle. The prevalence was highest in the groups migrating from high prevalence areas to Seattle (a high prevalence area) and lowest in the groups migrating from low prevalence areas to either city.

In order to investigate the reasons for this "age-at-migration effect" a case-control study was done on MS patients and matched neighborhood controls not born in Los Angeles. MS patients before age 20 were found to have had almost twice as many changes of residence as matched controls. This increased mobility among patients may reflect a greater opportunity for exposure to a single etiologic factor or for multiple exposures acting on a susceptible host. No differences were found between MS patients and controls in exposure to either small or large dogs.

The question of susceptibility was examined by studying the distribution of histocompatibility antigens in families with more than one case of MS. A preliminary study of 13 multiple-case families indicated that a single haplotype was associated with MS in all families, but that no single HLA allele was associated with MS in all these families. Some non-affected members of these families also shared the haplotype associated with MS indicating that penetrance was less than 100 percent and suggesting that additional factors beyond genetic susceptibility were necessary to cause clinical expression of the disease. Subsequent log of the odds (LOD) score analysis of a total of 45 multiple-case families supports the hypothesis of genetic susceptibility.

Studies of immunologic responses among patients and cohabitant controls confirm that MS patients have higher antibody titers to measles than controls, but also showed patients to have less competent cell-mediated responses to measles according to the Leukocyte Migration Inhibition test. Measles antibody titers and impairment of cell-mediated immunity to measles were lower among patients with the DRW-2 allele than among those patients without this allele. Humoral immunity to cytomegalovirus and herpesviruses 1 and 2 were similar between cases and

cohabitant controls, and cell-mediated immune responses to streptokinase-streptodornase (SKSD) not impaired, suggesting that the aberrant immune responses were specific to measles or an antigenically closely related virus (es). The lesser degree of immunologic impairment to measles antigen among patients with the DRW-2 allele and the higher frequency of this allele among patients may reflect selective survival mechanisms.

Studies are currently underway to: 1) investigate factors which cause genetically susceptible individuals to develop MS, 2) detect changes in immunologic responses in relation to clinical changes, 3) determine immunologic responses to other viruses, particularly myxoviruses, and 4) compare survival, rate of progression and disability among patients in high and low prevalence areas.

In Amyotrophic Lateral Sclerosis (ALS), also known as motor neuron disease (MND), impairment of the function of nerves controlling muscles (motor neurons) in the brain and the spinal cord produces progressive muscle weakness and wasting. It is caused by deterioration of a nerve fiber, and the demyelination is a secondary effect.

Up to 10,000 new Amyotrophic Lateral Sclerosis (ALS) cases are diagnosed each year. ALS begins in middle age, although some cases occur in the teens and some in 80's. While the disease is progressive and disabling, patients may live 3 to 5 years, and some reach a plateau and live 10 and rarely to 20 years. Weakness and atrophy of limbs, speech, and swallowing muscles follow pathological changes and death of related motor neurons of brain and spinal cord.

Unproductive therapies in the past have been guanidine, cobra venom, neurotoxin, corticosteroids, immunosuppressive regimens, immunostimulatory drugs, and transfer factor. At present, there is no effective treatment for ALS. Some drugs can be prescribed to relieve muscle cramping, and drugs such as belladonna or atropine are used to reduce excessive salivation.

The Neurological Disorders Program recently added two new grants supporting ALS research to its portfolio. The program staff is aware of inadequacy of research support in this area and is working actively to fill this gap. As a consequence of the length of the review cycle (minimum of nine months), we expect that more positive results from this activity will be reflected in future reports.

The symptoms of MND are associated with degeneration of the motor nerve cells. There is a progressive wasting and weakness of these muscles which lose their nerve supply, and signs of spasticity and hyperreflexia reflect the damage to the upper motor neurons. There are various clinical varieties described depending on the part of the nervous system which bears the brunt of the disease. The diseases, therefore, are referred to as motoneuron diseases or MND. As Brooke describes in *A Clinician's View of Neuromuscular Diseases*, "There is probably no more terrifying disease in the medical textbooks than the acute form of motor neuron disease. The appalling plight of the patient in whom a

rapidly progressive weakness of the arms and legs is associated with an inability to speak or swallow but whose mind remains clear to the end is obvious. The realization that MND is made up of a group of disorders which include progressive spinal muscular atrophy (ALS) has led to confusion about the prognosis and the pathogenesis of these diseases.

Motoneuron disease usually occurs sporadically in the population with a prevalence which has been estimated to be 2-7/100,000 population. Approximately 5 percent of the patients have a family history of the illness, and sometimes an autosomal dominant pattern of inheritance is seen. Males are more affected than females, with a preponderance of 1.6-2 to 1. Several retrospective studies have shown the mean age of onset to be between 46 and 56 years. The geographic areas of high incidence have included the Kii peninsula of Japan, Guam and the Mariana Islands, and the Kepi region of New Guinea. A low prevalence has been found in Mexico. MND, except in these particular areas, is said to account for 1/1000 deaths. The age-adjusted rate would be 0.6-1.2/100,000 population per year.

The clinical presentation is characterized by wasting, weakness, and fasciculations associated with hyperreflexia. Bulbar difficulties are also seen, but sensory abnormalities are not a major part of this disease. It is of particular interest that the cranial nerves III, IV, and VI are, with rare exceptions, spared as are bladder and bowel function. Urinary incontinence is a rare phenomenon, and sexual function is preserved.

Laboratory studies are helpful in the diagnosis of MND. Electromyography shows widespread fibrillations associated with giant polyphasic potentials and fasciculations. There may be slowing of motoneuron velocities, although they are typically normal. The use of muscle biopsy in the evaluation of patients with ALS can be helpful in early cases. Serum and cerebrospinal fluid (CSF) measurements of protein, sugar, and electrolytes are normal. Mononuclear cells are not seen in the CSF although in some cases abnormal numbers of cells have been reported. Serum creatinine phosphokinase (CPK) as well as other muscle enzymes may be increased to two or three times normal in about half of the patients.

Pathologic study of the central nervous system (CNS) shows degeneration of the large motoneurons in the ventral horns of the spinal cord and bulbar nuclei. There is also sclerosis of crossed and uncrossed corticospinal tracts. Posterior columns are spared except in familial cases. The nuclei of III, IV, and VI cranial nerves, and the medial sacral nucleus (S2) motoneurons in the spinal cord are spared. These findings correlate with the clinical signs.

There is, therefore, selective involvement of the motoneuron system. For example, anterior horn cells degenerate along with the pyramidal cells from which they receive synapses and the skeletal muscles which they innervate. The degenerative changes include shrinking, pyknosis, and excessive accumulations of lipofuscin. In addition to these findings, there are two other pathologic findings of importance: first, is the

so-called "dying-back" process with a predilection for the distal parts of the axon. In ALS patients, axonal loss is greatest in the distal regions of the long peripheral nerves and in the lumbar corticospinal tracts. This pattern of degeneration has been taken to indicate a "dying-back" process. The fact that characteristically ALS neurons show a "dying-back" process in the absence of central chromatolysis suggests that the molecular signal necessary for cell body reaction is not functioning properly. The second important observation is the presence of proximal axonal swellings which appear to be an important early lesion in ALS. These argyrophilic swellings are quite commonly identified in the anterior grey matter in both the classic ALS and in the familial cases. The argyrophilic inclusions have also been seen in Werdnig-Hoffman disease, a childhood motoneuron disease. The swellings contain large numbers of neurofilaments and tend to be present in regions showing recent clinical involvement. The swellings disappear as the motoneurons die, as they are rarely seen in end-stage disease when the majority of motoneurons have disappeared. These findings suggest that the neurofilament-filled axonal swellings in ALS are an early and important lesion in the human MND. It has been suggested that these swellings are the result of some abnormality in the dynamics of transport. The functional integrity of the nerves and the reciprocal interdependence between them and the target cells require an extensive exchange of molecular information. Such a complex molecular signaling system appears to depend on the normal operation of the axoplasmic transport system.

The only other pathological changes have been described as variety of "inclusions" and "bodies" within the cytoplasm of neurons from classical and Guamanian ALS cases. Included here were the findings of fibrillary alterations taking the form of ring-like or herring-bone arrangements. These changes were similar to those found in brains of patients in their 70's and 80's. Some of the Guamanian patients showed these changes as early as 28 or 29 years of age.

The etiology and pathogenesis of MND are unknown. The following hypotheses have been proposed. Heavy metal intoxication has been suggested as a possible etiology for MND. Lead intoxication may be present as a motor neuropathy in the absence of any sensory signs. Organic mercurial compounds have also been reported to cause MND in patients poisoned by a fungicide used on wheat. A more recent retrospective study involving a small number of ALS patients has suggested that a history of exposure to mercury and lead is more common than in controls. CSF lead levels have been reported to be elevated in ALS patients when compared to levels in normal subjects and other neurological disease controls, whereas plasma lead levels do not show as much change. Therefore, it is proposed that the normally efficient "trapping" mechanism performed by the erythroid series in the bone marrow is defective in ALS patients. A further hypothesis is that lead is more avidly taken up by ALS nerves than by normal nerves and transported by retrograde axonal flow with resulting neuronal cell body damage. Not all investigators report elevated lead levels, thus further analysis is required.

Aluminum has also been implicated. High concentrations of aluminum have been found in certain neurologic conditions such as Alzheimer's disease, progressive encephalopathies associated with industrial exposure, and in uremic patients undergoing hemodialysis. In addition, aluminum has been found experimentally to increase neurofilament concentration in neurons with the suggestion of impairment of axonal transport. This may be important since enhanced aluminum absorption from the intestine occurs with parathyroid hormone administration, and hyperparathyroidism is associated with MND.

Selenium toxicity has also been implicated. A preliminary report indicates that during a ten-year period, four cases of ALS had been found in a sparsely populated county (population 4,000) in west central South Dakota. The cases occurred in a region where naturally occurring selenium intoxication had been endemic in farm animals. However, this study has been challenged as not being a statistically significant focus of ALS.

Metabolic disorders are well known as a cause of neurogenic atrophy but not classical MND. Hyperthyroidism, insulinomas, hyperparathyroidism, steroid therapy, and hyperadrenalism have all been associated with motoneuron dysfunction. Defects of carbohydrate metabolism have been noted on several occasions in ALS patients. Abnormal glucose tolerance, tolbutamide tolerance and subnormal insulin secretion have also been found. Impairment of pancreatic exocrine function has also been reported with decreased neutral fat uptake, mild steatorrhea, and an abnormal response to secretin stimulation. These studies, however, have been disputed by others.

As mentioned above, neuromuscular involvement has been associated with hyperparathyroidism. The recent description of neurogenic atrophy associated with parathyroid adenomas and increased parathyroid hormone (PTH) deserves closer scrutiny. This is of interest since on occasion a patient with ALS has been found to have frank hyperparathyroidism and many patients with hyperparathyroidism have a MND-like abnormality. This is particularly important since one has to consider that PTH may increase the absorption of aluminum from the gastrointestinal tract. The association of these numerous toxic and metabolic disorders with a motoneuron-like disease is of great interest. Thus far, however, none of these factors have been found in classic ALS.

The chemistry of motoneurons as it might relate to ALS has recently been reviewed. Anterior horn neurons, for example, have a particularly high level of glucose-6-phosphate dehydrogenase (G-6-PD) and hence might have a greater capacity for the glucose shunt activity than other nerve cells. In ALS, G-6-PD was found to be normal. Others found that anterior horn cells had a relatively higher level of energy utilization than other spinal cord neurons. Alpha motoneurons appear to be richer in phosphorylase and in lysosomal enzymes than other neurons.

Studies of ALS and progressive muscular atrophy (PMA) have not shown any specific abnormalities. The only consistent finding has been that of

excess lipofuscin, a nonspecific finding seen in many conditions as well as in aging neurons. A decrease in oxidative enzymes, acetyl cholinesterase, thiamine pyrophosphate, and cyclic AMP and an increase in acid phosphatase was found in the CNS of ALS patients. A histochemical study of MND showed a decrease in two membrane enzymes, ATPase and 5 nucleotidase. It showed early abnormalities of the nucleus which suggests a progressive inhibition of DNA directed messenger RNA-synthesis. Some quantitative biochemical analyses on an ALS spinal cord from a Guamanian case were performed. Malic and lactic dehydrogenase, hexokinase, glutamic dehydrogenase, and G-6-PD, as well as hydrolytic lysosomal enzymes, were found to be normal. The normal G-6-PD levels in ALS were of interest because of the finding of a three-fold increase following axonal injury and during chromatolysis in normal neurons. These normal levels in ALS may indicate the inability of neurons to respond to the axonal injury.

Some suggestive abnormalities in the biochemistry of putative neurotransmitters have also been described. Spinal fluids of ALS patients have been shown to contain low homovanillic acid (HVA) levels. This finding was attributed to reduced dopamine synthesis in the CNS since the probenecid-induced accumulation of HVA was also reduced. Following L-Dopa therapy, there was a marked rise in HVA, but no clinical benefit could be determined.

Cyclic AMP has also been found to be low in spinal fluid of ALS patients as well as in patients with involvement of spinal motoneurons from other diseases such as those with spinocerebellar ataxia. Administration of a phosphodiesterase inhibitor to ALS patients has resulted in significant elevation of cyclic AMP spinal fluid levels. However, there was no clinical change. ALS patients do not have a low level of CSF cyclic GMP nor low serum levels of cyclic AMP or cyclic GMP. The low levels of cyclic AMP in the CSF could be due to neuronal death or could reflect an absence of a specific neurotransmitter. The most recent biochemical abnormality describes abnormal levels of free amino acids, such as tyrosine, and basic and aromatic amino acids in 12 ALS patients. These patients also had statistically significant elevations in CSF total basic amino acids including leucine. These findings are suggestive of defective membrane transport in the CNS.

The motor system is made up of neuronal-neuronal, neuronal-glial, and neuronal-muscle interrelationships. Cellular relationships have been postulated as being important in the synthesis and release of neurotransmitters, the expression and maintenance of receptors, and the generation of trophic factors necessary for the health of the motor unit. In primates, there is significant evidence that direct connections from the large pyramidal neurons exist in the motor cortex to alpha motoneurons in the spinal cord. The alpha motoneuron in the anterior horn also receives inputs from group Ia muscle spindle afferents, and the descending tracts from the vestibular nuclei, brainstem reticular formation, and the red nucleus. However, the major part of the synaptic input is from the poorly defined spinal cord interneurons. The putative neurotransmitters in the spinal cord have

not as yet been defined. Anterior horn cells have receptors for gamma-amino-butyric acid (GABA) and there is good evidence of postsynaptic actions of glycine, alpha alanine, beta alanine, taurine, aspartic acid, and glutamic acid. Only a few studies have been done in ALS patients to define the role of neurotransmitters, particularly their synthesis, release, and the state of their receptors. As stated previously, these included low HVA and low cAMP levels in CSF.

The questions related to function at the synaptic membrane have not been addressed at all. Reactive changes such as axonal sprouting have been described in ALS. Axonal sprouting can be the result of inhibition of transmitter release at the presynaptic membrane. Such is the case in botulinum and tetanus toxins where following denervation, regeneration occurs in the form of axonal sprouting from intact nerve terminals. The recently discovered "myasthenic factor" in bronchogenic carcinoma is also a presynaptic effect, but the long term effect on motoneurons is not known.

The questions relating trophic factors which influence the expression of receptors, the release of transmitters, and the general maintenance of neuronal health, have been largely limited to the developing nervous system. However, in recent years, attention has been directed to the mature nervous system. Changes in the peripheral nervous system, such as physical and biochemical axotomy and interference with neuromuscular transmission and muscle destruction, cause biochemical and morphological abnormalities in both developing and mature ventral horn cells. Axotomy also causes changes in the shape of excitatory postsynaptic potentials of motoneurons and failure of Group Ia synaptic connections. Axotomy has also been found to cause the loss of muscarinic receptors and the loss of synaptic contacts in the hypoglossal nucleus suggesting that the presence of receptors is necessary for the maintenance of the physical contact between pre and postsynaptic elements by acting as a trophic influence.

The feedback interplay between muscle and neuron is still to be defined. Some basic work has suggested that the contractile and metabolic characteristics of muscle fibers are tightly coupled with the biochemistry of motoneurons. Fast and slow muscle biochemistry is determined by the motoneuron. Rat motoneurons exhibit changes in the G6PD and acid phosphatase following repeated contraction and chromatolysis occurs in motoneurons of mice exhausted by swimming. Finally, it was found that the activity of choline acetyltransferase, the enzyme involved in the synthesis of acetylcholine, was significantly greater in combined cultures of spinal cord and muscle cells than in cultures of spinal cord cells alone. The increased activity of this neuronal enzyme is associated with the formation of functional neuromuscular junctions in culture.

The failure of transmitter release, receptor sensitivity, and trophic influences may all depend on intact axonal function. As described previously, the two suggestive findings implicating impaired axonal function in ALS are the presence of filament rich proximal axonal

swellings and the severe degeneration in the lumbosacral levels of the corticospinal tracts and the distal regions of motor nerves implicating a "dying back" process. In addition to these findings, Dapsone (4,4-diaminodiphenylsulfone), a drug used in skin diseases and leprosy, produces an axonal disease of motor nerves in humans. Recovery from drug related damage occurs by regeneration of axons and by peripheral sprouting of non-damaged axons. It was suggested that Dapsone produced a "dying back" phenomenon which impaired the soma and axons of the motoneuron.

Other MNDs which are related to possible axonal disease are B,B imidodipropionitrile (IDPN) intoxication and hereditary canine spinal muscular atrophy. In these two entities and MND chromatolysis, a reaction to axonal injury is a rare finding. This has led to many hypotheses that neuronal death in MND is secondary to the inability of motoneurons to respond to axonal damage. It is not known whether the failure to observe the classical changes of chromatolysis in most cases of MNS is due to the failure of the "signal" from the periphery to arrive or due to the inherent failure of the motoneuron to receive and translate the "signal".

The histocompatibility antigens determined by chromosomal HLA locus (HLA) complex in ALS has been explored in a variety of laboratories. HLA refers to all gene products controlled by the major histocompatibility complex region which is located on human chromosome 6. A variety of human diseases have been shown to be associated with the HLA. These are diseases in which an immune response process has been implicated, such as ankylosing spondylitis, psoriasis, multiple sclerosis, and diabetes mellitus. Myasthenia gravis has also shown an HLA association.

There have been numerous reports suggesting an increased incidence of a different antigen in motoneuron disease. An increase in A 3 in patients with ALS in the Boston area was reported. This association was not confirmed in ALS cases in the Glasgow area, but an increased incidence of A 2 and A 28 was found. In a study in Denmark, an investigator was unable to demonstrate a particular phenotype frequency pattern. Another investigator found none of these phenotype frequencies in Guamanians with ALS, but recently found an association with HLA Bw 35. Thus far, a clear pattern of HLA phenotypes or haplotypes has not yet emerged in studies of classical ALS patients.

A wide variety of immunologic indicators of disease have been studied. Neutralizing antibodies to poliovirus, mumps virus, and influenza virus were similar in ALS patients and controls as were antibodies to herpesvirus. Guamanians with ALS have similar levels of antibodies to herpesvirus, cytomegalic virus, and EB virus as compared to age and sex-matched controls. The immunoglobulin levels in twenty-one patients were found to be normal. Five of thirteen of patients in this study with PMA showing no evidence of pyramidal tract involvement did show elevated levels of serum IgM. The percent serum immunoglobulin in sixteen motoneuron disease cases was

higher than in eight controls, but not higher than in six patients with other neurologic diseases.

Immune complexes measured by the ClQ binding assay were demonstrated in the sera of ten of twenty-five ALS cases. In that study, renal glomeruli from nine of thirty-three ALS cases showed no IgG and C3. The deposited complexes after elution showed no immunologic reactivity to poliovirus. A similar study was done on sera from patients with ALS and Parkinsonism-Dementia (P-D) on Guam. Three of the five ALS patients and four of the twelve P-D patients showed significant binding of ClQ. Also circulating immune complexes were reported in ten percent of ALS cases using the Raji cell method of detecting immune complexes. There is, therefore, a suggestion that immune complexes are present in the sera of ALS patients but the nature of the antigenic component has not been clearly defined. Skin tests for delayed hypersensitivity were normal. It was stated that a generalized anti-inflammatory response had been noted in ALS patients. Skin testing of Guamanians with ALS and P-D to recall antigens showed diminished responsiveness. Diminished responsiveness to recall antigens has also been found in patients with bulbar ALS. In contrast to these studies, a whole host of immunologic studies in ALS patients to a variety of antigens such as basic protein, crude brain extract, and purified acetylcholine receptor have been negative. T and B cells have also been found to be normal. Total lymphocytes were reported to be elevated in ALS as compared to controls but not when compared to other neurologic diseases.

Serum factors have also been implicated in producing toxicity in vitro in murine anterior horn cells. In a follow-up study it was recently found that six of twelve ALS sera were positive; one of three normal controls were positive; all the three Duchenne muscular dystrophies were positive; and one of two spinal muscular atrophy sera behaved in a manner indistinguishable from the positive ALS sera. These studies could not be repeated. The factor in human sera which appears to be toxic to rodent anterior horn cells has not yet been identified.

The evidence for a viral theory of MND is not any clearer than the immunologic data. There are a number of reasons, however, to implicate viruses in the etiology and pathogenesis of MND. These include the following: 1) There are other noninflammatory, progressive degenerative CNS diseases due to viruses: Progressive multifocal leukoencephalopathy (PML), Creutzfeldt-Jakob disease, and Kuru. 2) ALS patients give a history of antecedent paralytic poliomyelitis at rates up to ten times that observed in control patients. 3) Many patients following paralytic poliomyelitis develop a slowly progressive, although for the most part, benign motoneuron disease. 4) A recent study of tissues from ALS patients suggests that there is a defect in DNA directed messenger RNA. A variety of viruses are known to interfere with host cell macromolecular synthesis. These include picornaviruses such as poliovirus, poxviruses, and some paramyxoviruses such as Newcastle Disease virus. 5) A transmissible C-type virus has been found to cause a type of motoneuron disease in the aging populations of a wild mouse colony.

6) RNA directed DNA polymerase (reverse transcriptase), an enzyme associated with oncornaviruses, has been demonstrated in the brain of Guamanian ALS patients and "normal" controls, but not in American ALS patients. 7) Picornavirus-like (poliovirus, coxsackieviruses, and ECHO viruses) crystals have been seen in muscles of a single patient with ALS.

Transmission of the disease to primates by inoculation of brain homogenates from ALS patients has failed. Isolation of virus failed after explanting, maintaining, co-cultivating, and fusing of non-neuronal CNS tissue from ALS patients. A comprehensive study was carried out on ALS patients in the Los Angeles area including serological evaluation for antibodies to mouse neurotropic C type virus, mouse leukemia agents, Gibbon ape leukemia virus, and endogenous type C virus of domestic cat; all were negative. Furthermore, examination of ALS tissue for the presence of antigen to mouse neurotropic C-type, electron microscopic examination of anterior horn cells, transmission of ALS tissue to mice, explantation of tissue into culture, and rescue techniques did not demonstrate mammalian type C virus in human ALS. A large number of the above described problems are being studied by a group at the University of Southern California.

Clinical studies at St. Vincent's Hospital and Medical Center of New York of 98 ALS patients with quantitative muscle testing established slow, moderate, and fast stages. Immediate postmortem of 23 ALS patients were performed. Histological and electronmicroscopic studies confirmed unique proximal giant swelling of CNS neurons. Immunopathology showed immune complex deposits in astrocytes of the CNS. These cells functionally and mechanically support neurons and their injury or altered activity due to antibody could affect neurons.

The immunological assessment of ALS patients showed cell-mediated immunity to tuberculin was not depressed. Assay of blood T and B cell numbers and functional responses to standard antigens and stimulating substances were not different from controls. Lymphokine production (a measure of T cell function) in the presence of specific antigen such as tuberculin was not decreased. Humoral antibody (IgG, IgA, and IgM) levels and complement levels were similar to other neurological disease controls. Histocompatibility studies showed a decrease in incidence of HLA-9 antigen.

Association of poliomyelitis with ALS has been suggested. Serum antibody response to poliomyelitis virus, however, paralleled control populations. However, in vitro cell-mediated immunity to poliomyelitis virus was found to be greater in ALS than other neurological disease controls, approaching that of vaccinated normals. The influence of polio vaccination on the incidence or course of ALS is not known at this time since the vaccination program began in the 1950s and vaccinated persons have not reached the age when this disease generally becomes manifest. The possibility that brain tissues of ALS patients becomes antigenic and causes development of autoimmunity to neuronal material was also studied. It was found that ALS patients had increased cell-mediated immunity to the isolates of ALS brain.

The viral isolation and co-cultivation studies of postmortem tissue and analysis of humoral antibody responses of ALS patients suggested a relationship between adeno-associated virus and ALS. This virus did not cause cytopathic changes when injected intracerebrally into neonatal mice. Antibody extracted from kidneys of ALS patients showed no viral specificity with known viruses except 1 out of 9 ALS cases had antibody to poliovirus. Studies continue on parvo and picorna (polio) viruses with explant cultures and neurons isolated by gradient centrifugation.

Gangliosides are lipid materials present in membranes of neurons which act as receptors for various toxins, e.g. cholera toxin. An abnormal distribution of gangliosides was found in the sensory and motor areas of the frontal cortex of ALS patients. The nerve culture program confirmed neurocytotoxic factors in ALS sera in culture of mouse spinal cord nerve cells. Similar serum factors were found in other neurological disease controls and individuals in contact with ALS patients. Neurocytotoxicity was most marked with ALS sera showing a difference in specificity. The serum factor was present in all stages of ALS. Correlations of these laboratory investigations with clinical state and the stage of the disease by showing cause-effect relationships may point to specific therapy for this serious disease.

The greatest hindrance to our understanding of the MND is the lack of suitable experimental models. Recently, the mutant Syrian hamster, showing hind leg paralysis has been discovered at Montefiore Hospital and Medical Center, and is utilized in a study to assess its correspondence to certain human neuropathies, specifically ALS. The study has centered on the electron microscopic changes of peripheral axons and their coverings, the myelin sheaths. Several alterations have been observed. These studies are being continued in an effort to understand the relationship of these morphological changes to each other and to the symptoms they produce.

Work is in progress on mouse encephalomyelitis virus which serves as an experimental model of ALS. At the Johns Hopkins University two experimental models: hereditary canine spinal muscular atrophy (HCSMA) and Beta-Beta-Imidodipropionitrile (IDPN) show pathological features in common with ALS.

Research in genetics, specifically on human leukocyte antigens (HLA) found first to be important in transplantation, is relevant in MS and ALS, and is one of the research approaches carried out by a number of investigators. In MS and ALS patients, as has been stated previously there is overrepresentation of certain HLA determinants with respect to the normal population and, furthermore, the HLA antigens could be further differentially associated with rapid and slow ALS progression. However, no clear-cut conclusions as to the relevance to the pathogenicity can be drawn.

Muscular and Neuromuscular Disorders

Muscular and neuromuscular disorders are directly responsible for disability in patients with many diseases of the central and peripheral nervous system. Research on the pathophysiology and treatment of these disorders is a major portion of this program's extramural research support portfolio. Presently the Neurological Disorders Program is providing research grant support for 135 projects in the amount of \$11,331,000. During the period covered by the Annual Report the NINCDS received 92 applications for research in this area of which 72 were approved and 46 were funded. Included were research projects related to muscular dystrophy, myasthenia gravis, the peripheral neuropathies, and other disorders of movement. We are fortunate that one of these disorders, myasthenia gravis, is demonstrably controllable. We hope that ultimately the other disorders will be responsive to intervention. Three grants are specialized research centers (neuromuscular diseases) and one, a program project, is primarily concerned with the pharmacology of neuromuscular disorders. Most of the regular research grant support is for basic studies of the neuromuscular system. When we categorize the individual research grants and the separate components of the centers according to the primary research interests of the principal investigators, we find a relatively flat distribution of efforts among the various aspects of the neuromuscular system. There is currently a wave of interest in synaptology and properties of normal and diseased membranes. Another focus of interest is muscle physiology and motor control. Much of this is classic electrophysiology of both individual units and aggregated systems of motor units. The latter adds to our knowledge of how muscles work in concert. Two other foci of research activity are pathophysiology, protein synthesis and metabolism of muscle tissue.

Synapses are excellent structures for investigating the cell biology of secretion, which operates in them by exocytosis as it does in other gland cells. Using electronmicroscopic techniques one investigator has photographed neuromuscular junctions that have been frozen rapidly at different moments before, during, and after single nerve impulses. He has successfully imaged neurotransmitter secretion and uptake across a synapse. This research is progressing and we expect to learn more about the process of transneuronal transmission from these data.

Other studies have shown that apparent synaptic potentials seen in axons behave in a manner consistent with a model of "backward" coupling across synapses. One study deals with "seizure" activity of cells in the spinal cord, which is accompanied by prolonged depolarization of the reticulospinal axons. Another focusses on characteristics of presumed chemical inhibitory and excitatory synaptic potentials. Both the prolonged depolarization and the synaptic potentials have characteristics usually attributed to chemical transmission. Because responses are dependent on membrane potential it has been assumed that they involved a chemically mediated conductance change. Analysis of these data suggest that both the prolonged depolarization and apparent

excitatory synaptic potential amplitude varying with membrane potential can be explained quantitatively by the intrinsic properties of the axons. Thus, current arriving in an axon from other cells through electrical junctions produces a relatively large depolarization if the axon is hyperpolarized and a much smaller depolarization if the axon is depolarized, simply because of changes in axon resistance. The paradox of apparent chemical synaptic potentials without the morphological presence of adequate numbers of appropriate synaptic connections may thus have been resolved.

A series of studies of cortical motor potentials in man and monkey are almost completed. In the macaque a self-paced hand closure is associated with a slow potential in the motor hand area, and area 6 adjacent to the midline. The potential in the motor hand area precedes the onset of movement and has the earliest latency of any of the potentials recorded from these 3 areas. In man, the areas mentioned above also show a slow potential, but in addition, the slow potential is recorded in an area of cortex anterior to area 6. Studies on motor potential in humans have been carried out in epilepsy patients undergoing surgery for seizures intractable to medical therapy. One interesting observation was a lack of electrical excitability of motor cortex for producing movement in children between ages 1 1/2 to 4 years. This has been ascribed to immaturity of the cortex. There may be disparity in ontogenic development between sensory-evoked responses and cortically-induced movement.

Other studies underway add to our knowledge about the way motoneuron pools are organized and controlled. It is known that the organization is changed in neurological disease or trauma, however, current knowledge of the normal organization is not yet adequate to allow changes to be used as a diagnostic tool. Studies of normal motor pool organization will allow a better understanding of how motor units and muscles with very different mechanical properties are integrated into smooth movements. Some results obtained during this year contribute to the current controversy regarding recruitment order in different muscles. It was shown that this recruitment order is not as stable in response to mixed inputs as it is to the homonymous spindle input generally studied. This could explain reversals in recruitment order previously reported. Studies of rank-order of the entire pool, however confirm a general pattern of recruitment order according to motoneuron size. The one clear reversal of this pattern appears to be a presynaptic effect and not a result of direct facilitation by large motoneurons.

Human studies have shown that muscles may be controlled in different ways. Force in biceps is graded strongly by recruitment of units throughout the force range while rate coding is less precisely controlled. Adductor pollicis motor units are all recruited at lower force levels, and the frequency of spike trains is precisely controlled. Irregular discharge patterns of motor units would strongly affect force output of this muscle at high force levels, since rate coding is apparently the sole mechanism of force modulation.

Another research project utilizes experiment, computer simulation and analysis to study the coordination of muscles during propulsion by animals and human subjects in the execution of a jump. Jumping was chosen because of its

suitability for analysis by a combination of experimental measurements and optimal control techniques and because it is a good starting point for a deeper study of neural and muscular control of movement. The quantitative methods developed will be useful later in the analysis of human gaits. Long term goals are to use these quantitative techniques to develop rehabilitation systems for the physically handicapped and quantitative tests for the evaluation of physical dexterity in patients to assess drugs and other therapeutic programs.

The use of behavioral technologies in the management of patients with neuro-muscular and convulsive disorders is expanding rapidly. The Neurological Disorders Program is cooperating with the Johns Hopkins School of Medicine and the John F. Kennedy Institute for the Handicapped in sponsoring a conference in 1980 to develop a state-of-the-art report on progress in the use of behavioral therapies for the alleviation and control of these and related disorders. The emergent report will be published and distributed widely so that researchers and practitioners can avail themselves of state-of-the-art behavioral techniques.

Muscular Dystrophy

Muscular dystrophy refers to myopathy with two characteristics: a genetic basis and progressive weakness. The exact causes of the degenerative changes in the muscles are unknown. However, there appear to be disturbances in the enzyme systems concerned with muscle metabolism. Significant pathological findings tend to be confined to the muscles although the ventral horn cells have been shown to be degenerated or reduced in number. There is no treatment which has proved to be effective in arresting the course of the disease. Grant support for research in this area is comprised of 16 research grants, portions of three clinical research centers and one program project, in the amount of \$1,678,000.

Duchenne muscular dystrophy (DMD) is the best-defined of the muscular dystrophies. It is inherited as an X-linked recessive characteristic with complete penetrance. Female carriers are usually asymptomatic but evidence of the carrier state may show up under laboratory testing.

Progression of the disease is rapid, usually being diagnosed at 3-6 years of age. Patients usually do not walk beyond 10-12 years of age. In fact, inactivity by the patient usually results in an inability to walk ever again. Cardiac muscle involvement occurs in almost all patients and there is a high frequency of mental retardation.

Theories of etiology emphasize the importance of one or another organ system, for instance, defective neurons or vasculature. However, neither neurogenic nor vascular theories have not been well-supported. One possible explanation in DMD, as in other genetic disorders, is a widespread independent expression of a metabolic defect in many tissues. Muscle may be the principal target because the biochemical defect most affects the function and integrity of this tissue.

It is probably correct to reason that, as with other recessively inherited genetic disorders, the disease is due to mutation in a single enzyme or a small number of enzymes with similar amino acid sequences near the active sites in the enzymes. The descriptions in recent years of structural or biochemical defects in cell membranes or erythrocytes, platelets, and muscle suggest that the enzymatic defect is expressed subcellularly by a change in cell membranes.

The research interest of some investigators has been with properties of cell membrane in Duchenne dystrophy. They have mostly studied adenylyl cyclase, an enzyme which localizes to plasmalemma and which reflects changes in plasmalemmal biochemistry. They have also demonstrated changes in cells other than skeletal muscle. The focus is currently on biochemical properties of adenylyl cyclase in Duchenne tissues, to determine whether enzyme, receptor, or membrane environment is abnormal.

The membrane theory of Duchenne dystrophy attributes the increased serum enzyme activity to abnormal permeability of muscle cell surface membranes. However, this has never been shown experimentally. Investigators are studying enzyme release from isolated blood cells and cultured Duchenne muscle. Erythrocyte membrane properties are also studied by biophysical methods.

Optimal conditions have been established for enzyme release in muscle culture and one Duchenne culture, the only one so far studied, showed abnormal leakage. Since muscle cells in tissue culture resemble normal fetal muscle in many respects, increased enzyme leakage in Duchenne may be present at a early stage of differentiation. Studies of enzyme leakage are continuing in order to determine the cause of contractile protein abnormalities in development. In addition, investigators are extending analyses of steady-state tension responses and incorporating tests for fast and slow twitch fibers into studies of human muscle disease.

The major clinical manifestation of Duchenne dystrophy is progressive muscle weakness. This weakness is usually attributed to necrotic loss of muscle fibers; in vitro analysis of Duchenne muscle has indicated that the intrinsic strength of the contractile proteins in most Duchenne fibers is less than normal. Biochemical, immunochemical, physiologic and ultrastructure studies strongly suggest the most likely cause of the low tensions to be structural disorders in the myofilaments.

A number of structural abnormalities in non-necrotic fibers from Duchenne muscle, however, have been reported and some of them could reduce the ability of the contractile proteins to develop tension. Of particular interest are those described as a shortening or lengthening of sarcomere spacings without loss of contractile material.

A diffuse decrease of internal membrane particles in the freeze-fracture plasma membrane has been described in Duchenne dystrophy. Expression of this defect in cultured muscle cells would be of considerable theoretical interest because it would indicate a genetically determined abnormality inherent in the muscle cell, possibly in the plasma membrane.

Investigators have measured maximum force (P_o), sensitivity to substrate, and Ca sensitivity, in over 200 single human skinned fibers. They found that P_o was significantly less than normal in the majority of fibers. The data on P_o provide the first direct evidence that muscle weakness involves a defect in contractile protein function before significant loss of muscle mass has occurred. The investigators have postulated that low tension in single skinned fibers prepared from Duchenne muscle are linked to structural disorders in the sarcomeres. More specific tests of this hypothesis are planned.

The differentiation of skeletal muscle involves cell recognition and fusion. This together with the hypothetical existence of a membrane defect in muscular dystrophy, has led workers to examine the topography, composition, and metabolic turnover of plasma membrane proteins in differentiating cultures of normal and genetically dystrophic embryonic chick breast muscle. No topographical differences were found between normal and dystrophic fibroblasts, myoblasts, or myotubes.

Another group of investigators is attempting to characterize the cellular and humoral immunodeficiencies in the Storrs strain of muscular dystrophic chickens, and to establish the relationship of the immunodeficiencies to the pathogenesis of the muscular dystrophy phenotype. PAGE (polyacrylamide gel electrophoresis) and IEF (isoelectric focusing) analyses of the soluble fraction from the pectoralis major and the posterior latissimus dorsi of muscular dystrophic chickens reveal quantitative protein and isozyme differences when compared to normal age and sex matched controls. These procedures hold promise as one element of a pathological index established on the bases of several different parameters. Finding two major genetic disorders, muscular dystrophy and immunodeficiencies, in the Storrs strain of muscular dystrophic chickens may be important. On the basis of immunogenetic analyses of the two disorders, the investigator shows that the two traits are genetically separable, and postulates that the time of onset and degree of severity of the muscular dystrophy phenotype is altered in the absence of the cellular immunodeficiency. This points up the importance of genetic studies in interpreting data on common membrane defects such as those seen in human myotonia and Duchenne muscular dystrophy. These studies suggest an important role for the immune response in myopathies. Perhaps if the immunodeficiency is corrected or alleviated it could have a beneficial effect on the muscular dystrophy phenotype.

Other work is directed at the muscle surface membrane as a possible location of the primary defect in several of the muscular dystrophies, and this membrane hypothesis has received particular support in the case of the myotonic disorders. There is evidence for biochemical abnormalities in the muscle sarcolemma and RBC membrane in patients with myotonic dystrophy, and there are convincing data that the myotonic phenomenon itself is due to a conductance abnormality in the surface membrane.

Myasthenia Gravis (MG)

MG is a chronic neuromuscular disease characterized by progressive weakness and abnormally rapid fatigue of the voluntary muscles. The disease tends

to be contracted at earlier ages by females and at later ages by males. There have been, in recent years, progressive improvements in the management of patients with this disease. These have been in hospital care, technical improvements in respiratory support devices, steroids and wide use of tracheostomy. Impressive use of anticholinesterases, the preferred treatment for many years, has made it possible to relieve symptoms for many afflicted victims. The anticholinesterases facilitate transmission of nerve impulses across nerve-muscle junctions to activate muscles. In MG, transmission of the nerve-muscle impulse is defective. ACTH and prednisone are believed to suppress the immunologic abnormality believed to be responsible for the transmission defect. Not too many years ago, MG patients died within the first few years of their illness. Today, under proper supervision, many can live virtually normal lives.

The Neurological Disorders Program has awarded 14 grants in the amount of \$1,253,000 for the study of myasthenia gravis.

Some investigations of the pathogenesis of myasthenia gravis (MG) have been directed toward relating the mechanisms of action of humoral antibodies to the clinical severity of MG in individual patients. Since the number of ACh receptors is decreased in MG skeletal muscle motor endplates, two important mechanisms that may be important in producing this effect are: 1) decreased synthesis of ACh receptors, and 2) accelerated degradation of ACh receptors. Accelerated degradation of ACh receptors in myotube cultures has been previously demonstrated in adult synapses. Investigators have demonstrated that MG serum or immunoglobulins decrease incorporation of new ACh receptors into myotube culture surface membranes.

Additional research addresses the relevance of the effects of humoral antibodies in determining the clinical state of individual MG patients. Several studies were carried out during the past year. Findings include: 1) Anti-ACh antibody titers do not correlate with clinical severity of disease in the populations of MG patients and do not necessarily correlate with changes in clinical myasthenia in individual MG patients. 2) Presumably identical anti-ACh receptor antibodies can have markedly different clinical effects in different individuals. 3) The degree of acceleration of ACh receptor degradation produced by MG immunoglobulins correlates only with the titer of anti-ACh receptor antibodies and not with the clinical state of MG patients. Future work will be toward investigation of decreased incorporation of new ACh receptors and the role of "host" factors in determining the severity of clinical myasthenia in MG patients.

Drug therapy such as long-term, high-single-dose, alternate-day prednisone, perhaps coupled with thymectomy, which removes a source of antibodies considered a major factor underlying impaired neuromuscular transmission, may make MG the most successfully managed neuromuscular disorder.

The technique of plasmapheresis is being used to remove antibody from the blood of MG patients. A bypass is introduced into the patient's blood system so that blood can flow through a continuous centrifuge. This separates the cellular components of the blood from the soluble fraction,

the plasma. The cells are then allowed to re-enter the circulation with fresh plasma or plasma substitute. The technique allows the replacement of the entire plasma of the patient without disturbing the important cellular components of the blood. Unfortunately, the antibody slowly returns. It is generally only used for severely afflicted patients.

Another approach to the study of MG involves the effect of the myasthenic process on the endplate and the muscle type. Current data confirm earlier results that the myasthenic process leads to a deficit of cholinergic transmission. They also support the concept that the myasthenic process leads to a change of endplate properties.

Understanding the structure and function of the acetylcholine receptor (AChR) is important because the AChR is an archetype for studying neurotransmitter and drug receptors in the peripheral and central nervous system. In particular, understanding the structural basis of AChR function may provide a molecular explanation for neuromuscular transmission, may help to provide a more rational basis for drug design, and may help explain developmental processes in synapse formation before innervation and after denervation. Immunochemical studies of AChR structure and function can help also to bridge the gap between the many systems used to study various aspects of AChR structure. Study of experimental allergic myasthenia gravis (EAMG) has proven its importance by providing a model for illuminating the once inscrutable pathological mechanisms of MG. It continues to be valuable as a model for study of pathological mechanisms and for studying therapy. In addition EAMG is valuable as a tool for producing anti-AChR and studying their effect *in vivo* on AChR function and metabolism. Understanding the pathological mechanisms in MG and EAMG are important not only as ends in themselves, but as models for other autoimmune anti-receptor diseases such as those recently identified involving receptors for insulin and for anti-receptor and other anti-surface membrane component diseases yet to be identified.

Electromyographic studies in cases of congenital myasthenia syndrome demonstrated a repetitive response of the compound muscle action potential to stimulation. In vitro studies of intercostal muscle biopsies revealed an abnormal prolongation of the duration of the miniature end-plate potentials (mepps) and end-plate potentials (epps). This could have been due to a lack of end-plate acetylcholinesterase (AChE) or to an abnormally prolonged open time of the Ach-induced ion channels. Detailed ultrastructural and electroncytochemical studies are being done on the biopsies pertaining to the localizations of AChR, antibody and complement components at the end-plate and the ultrastructure of the end-plate is being analyzed by morphometry. These studies will help in differentiating an abnormality of Ach-induced ion channels from autoimmune MG and from previously described myasthenic syndromes.

Peripheral Neuropathies

There are approximately 3 1/2 million diabetics in the United States. Approximately 10% of these have symptoms of painful burning, numbness, weakness, or paralysis, or more serious symptoms. The causes of these symptoms

are not known and treatment does not exist. In recent years, people afflicted with these diseases has resulted in the Neurological Disorders Program placing a special emphasis on research in this area. There are only a limited number of regular research grants focused on these problems; however, a year ago the NDP awarded a specialized research center grant to the Mayo Clinic and Foundation in Rochester, Minnesota. The center coordinates multidisciplinary research on human and experimental neuropathies, with the intent of elucidating their causes and, hopefully, eventually developing treatments. Investigators are focusing on new approaches and techniques that combine morphologic, electrophysiologic, immunologic, biochemical, and physical research techniques. With an intimate intertwining of basic research and patient care, future prospects are bright. A system has been developed to quantitate the capabilities of sensory modalities in man. There are a number of morphometric studies applied to human and animal biopsy, and autopsy material. Electrophysiological studies of nerve function include the usual clinical methods as well as attempts at innovation, for instance, single fiber investigation in vitro. There are studies of abnormalities of axonal flow and endoneural pressure. Immunologic methods are being used to assign cellular responsibility for segmental demyelination and to assess the roles of viruses in inflammatory neuropathy. Studies of lipid composition of nerve and the effect of modification of membrane lipids are to be undertaken by lipid chemists. The largest single responsibility of the center will deal with diabetic neuropathies; however, other neuropathies to be explored include a number of genetically determined diseases in man and animals, human and experimental heavy metal intoxication, and inflammatory diseases. One ongoing study of note asks whether there is an accumulation of alcohol sugars in damaged fibers in diabetes. Another, whether there is a decrease in myoinositol in peripheral neurons. The issue is that diabetics are not "tightly controlled" in regard to blood sugar levels in order to avoid hypoglycemia. There is a concern that the increased blood sugar levels interfere with neuronal metabolism. Animal studies are underway and 12 humans and controls are being evaluated on "tight" blood sugar levels vs. "usual" diabetic therapeutic levels.

With respect to work on the Guillain-Barre Syndrome, researchers report that several findings have important implications for future research. It was found that rats are a far more suitable animal to study experimental allergic neuritis (EAN), a model for Guillain-Barre Syndrome, than rabbits, guinea pigs or monkeys; further, the P2 protein is the neuritogenic antigen, not alone, but as a lipid-protein complex, and, antibody to P2 protein was produced and used to localize the P2 protein in peripheral nerve myelin. It is hoped that EAN (experimental allergic neuritis) will eventually rank along with EAE (experimental allergic encephalomyelitis) in differentiating events in autoimmune disease in detail and serve to help us understand the induction and possible suppression of the Guillain-Barre Syndrome in humans.

Infectious Diseases

This program supports investigations of a variety of slow or persistent viruses and viral infections. The research is targeted or relevant to the elucidation of the etiology or pathogenesis of multiple sclerosis, amyotrophic lateral sclerosis, and abnormal aging, among other neurological disorders.

In the fiscal year 1978, 28 grants were awarded for which support was \$1,812,155. A total of 32 applications were received of which 9 new and 8 competing renewals were funded with an expenditure of \$538,252 for new and \$503,902 for renewal grants. As of July 1, 1979, this program supported 33 research projects with a total investment of over 2 million dollars.

A variety of diseases involving the central nervous system (CNS) are disorders of unknown cause. Many of these diseases may be the result of virus infections. It is suspected that these disorders may arise from what is termed a "slow virus" infection. In this case, the actual virus infection may occur years before the disease actually manifests itself. It is likely that not all people infected with the virus actually develop the disease. It is also likely that a variety of factors can stimulate an infected person to develop the disease. These characteristics would make it difficult to pinpoint a single event as a cause of the disease and dictates that a multidisciplinary approach must be used in order to accurately pinpoint the cause or causes of a disease. It is thus of interest to examine particular CNS diseased tissues as well as normal tissues for the presence of specific viruses. To do this a highly specific and sensitive method for detecting the presence of a specific virus must be utilized. It is not known how many CNS cells need to be infected with virus to produce a diseased state. It is likely that a small fraction of cells in a crucial area could disrupt neural function. It is imperative then that any test for detecting virus be as sensitive as possible. One virus particle can easily be detected if it can grow and amplify itself into many viruses. This is obviously the most sensitive test possible. The inability to recover a growing virus from a tissue does not mean, however, that a virus is not present in the tissue. A virus may be able to perpetuate itself in the cells of the tissue but be inherently defective in its ability to produce an infective virion. This virus may alternatively be perfectly capable of forming large numbers of highly infectious virus progeny. It may be in a latent state, however, and need a particular stimulus to set it growing. Unless the right stimulus were used, this virus would remain undetected by the growth assay. Another virus might be particularly labile and be inactivated by sitting in dead tissue for even a short time. Obviously, the virus detection method used for these studies must be highly sensitive, specific and flexible in its ability to detect the virus' presence no matter what form or state of activity the virus is in.

One portion of the virus, the viral nucleic acid, must be in the tissue if the virus is present at all. Consequently, nucleic acid hybridization

provides a highly specific, extremely sensitive test for the presence of defective or competent viral nucleic acids, even when there are no viral gene products or infectious viruses present in the tissue.

In order to detect viruses as sensitively as possible, an investigator at La Jolla Cancer Research Foundation has: (a) developed methods to produce various radioactive viral nucleic acids to be used as probes to specifically detect the presence of certain viruses in the CNS tissue; (b) modified nucleic acid hybridization methods in order to increase the sensitivity of virus detection; (c) made basic discoveries in the area of nucleic acid hybridization which should allow an increase of the sensitivity of viral detection by 100-1000 times. The modified test currently used will specifically detect the presence of one copy of virus RNA per 300 cells when one gram of tissue is used in the assay. The best radioimmune assays will detect about 10-15 moles of antigen while the hybridization method will detect the presence of 10-18 moles of virus RNA. These methods will be used to examine Multiple Sclerosis, Amyotrophic Lateral Sclerosis and Parkinson's Disease tissue for the presence of measles virus, polio virus and influenza virus. Evidence has suggested that these viruses may be implicated in these diseases.

The infectious diseases program encompasses some of the very exciting work in neurology today, because most of the work here is in the area of slow viruses. Therefore, a discussion of "slow" viruses and latency is appropriate.

In recent years the concepts of "slow" and "latent" virus infections have assumed great importance in the study of neurological diseases. Kuru and Creutzfeldt-Jakob disease were found to be caused by transmissible virus-like agents, while more conventional viruses were isolated from individuals with subacute sclerosing panencephalitis and progressive multifocal leukoencephalopathy. Study of a possible viral etiology of Multiple Sclerosis continues, with several viruses being intensively investigated. In addition, viruses in the herpesvirus group have been found by a number of investigators to be "latent" in nervous system and other tissues of asymptomatic individuals. Thus, the varicella-zoster virus may be "latent" in dorsal root ganglia of the spinal cord and the reactivation cause clinically apparent herpes zoster. Human cytomegalovirus, another herpesvirus, may remain latent and be activated with immunosuppression in renal transplant patients, and Epstein-Barr (EB) herpesvirus may be "latent" in lymphocytes of individuals who have had infectious mononucleosis. In studies of herpes simplex virus (HSV), infectious virus has been isolated from the trigeminal and dorsal root ganglia of "latently" infected humans and from experimental animals similarly "latently" infected with the virus. In one study "latent" HSV infection of the trigeminal ganglion was found in 50 percent of unselected individuals at autopsy. The relationship of "latent" ganglionic infection to HSV encephalitis, trigeminal neuralgia, or atypical facial pain, has not yet been established. However, since herpes is a frequent "latent" virus infection of the human nervous system, investigation of "latent" HSV infection of the trigeminal ganglion is of considerable importance.

"Latent" infections will be discussed below in operational and in theoretical terms. A "slow" virus infection may be considered to indicate a clinically slowly progressive, subacute or chronic virus disease, and one which may or may not have been initiated by a previously latent virus. It would be difficult at present to provide a single all inclusive definition of latent virus infections, but several points may be considered in discussing viral latency. In vivo latent infection is probably subclinical or inapparent, and likely to be long-term or chronic. A latent infection may be dynamic, in that the virus is being replicated, or static, that is, without virus replication. If the absence of infectious virus were considered most important to the definition of latency, virus infections in which small amounts of virus are continuously or periodically replicated would not be considered latent infections. Important to the consideration of latency is the possibility that with present techniques virus cannot be isolated or identified in infections in which there is only a small amount of complete virus present. But efforts in this direction are in progress.

Infections with continuous, although possibly low, levels of virus replication might be considered to be persistent rather than latent. Infections in which infectious virus is occasionally or periodically produced, however, might be considered to be due to occasional viral reactivation of a true latent infection. Virus characteristics and pathogenesis of infection would probably be very different among these types of infections. The concepts of static and dynamic infection, however, may provide a valuable framework upon which latent virus infections may be placed, particularly latent in vivo infections, in evaluating virus characteristics and pathogenic mechanisms.

The experiments in recent years on nucleic acid hybridization and re-naturation kinetics have been used to determine the presence of viral nucleic acids in transformed and neoplastic cells. Virus infection of transformed cells, such as those transformed by HSV, may be considered to be latent in that at least some viral DNA sequences are present while infectious virus and intact virions are not. While similar mechanisms may be involved in establishing latent HSV infections of sensory ganglia, it would be premature to arrive at this conclusion at present. Latent HSV ganglionic infections may involve mechanisms other than transformation whereby "true" (i.e., static) latency is achieved. Most experimental evidence of in vivo HSV latency would be consistent with a static infection, however, the data do not at all rule out the presence of a low-level dynamic infection. Further study of latent HSV infections of sensory ganglia is clearly required to clarify this point.

In a dynamic latent infection the virus may be complete or incomplete, such as temperature sensitive (ts) mutant virus. In a static latent infection viral DNA may be integrated into host cells and possibly covalently linked with host DNA, or present as an episome; the latent infection, therefore, may be similar to that of HSV infection in HSV-transformed cells or EB virus infection of African Burkitt lymphoma

cells. The existence of a static or dynamic latent infection would determine whether virions could be seen by electron microscopy; observation of virus particles would be more likely with a dynamic latent infection. Also, with a dynamic latent infection viral antigens might be expected to be visualized in latently infected tissue if fluorescent antibody techniques of sufficient sensitivity were employed. In cases of static infection fluorescent antibody testing may also be positive when virus-induced antigens are present on cells. Finally, as in studies of latent HSV infection of sensory ganglia, the methods necessary to achieve virus isolation may be considered important in reflecting the status of the latent viral genome. The requirement for co-cultivation of latently infected ganglia with indicator cells, and the inability to isolate virus from cell-free extracts of latently infected tissues, may indicate viral integration into the host neurons (probably static infection). Alternatively, this requirement might be consistent with a dynamic infection in which defective virus was being produced. Consideration of the presence of cell-associated virus, however, cannot be overlooked in evaluating any requirement for co-cultivation.

Other possible criteria to define latent virus infections also exist. Thus, multiplication of latently infected cells, without any evidence of virus proliferation, which may indicate covalent integration of viral DNA into host DNA, may be used as a criterion. Since, however, mature neurons in vivo do not multiply, this possible criterion will not be considered in discussing latent HSV infection of ganglionic neurons. One or more of the above criteria may be important in defining latent virus infections.

The study of the pathogenesis of a slow virus disease as it progresses in animal models is particularly important. The analysis of slow viruses of man, Kuru, Creutzfeld-Jakob, has been paralleled by the discovery of animal slow virus diseases. Investigators on the West Coast are studying scrapie and also VISNA in collaboration with an extensive program at Johns Hopkins University. Experimental Creutzfeld-Jakob disease has been developed in laboratory animals by investigators at Yale University.

Despite of the lack of a success in direct efforts to isolate putative MS and ALS causative agents, the discovery by Gajdusek, Gibbs, and their co-workers of the transmissible nature of Kuru and the long latency time between the ingestion of the agent and the development of the disease have spurred efforts in this area. The mechanisms by which a virus might attack an organism, either a human being or an experimental animal, and cause a disorder which persists, while exhibiting no significant symptomatology at the time of infection, but reactivated or released from latency many years after the initial insult, is clearly important. Therefore, the mechanisms by which these viruses can persist are being actively investigated by grantees from NINCDS.

An obscure disease of sheep called "scrapie" has been an important area of biochemical research. Transmission studies and neuropathological

examination of brain tissue suggest that scrapie is a prototype for the spongiform encephalopathies of man, i.e., Kuru and Creutzfeldt-Jakob disease. Prior to the transmission of the Kuru and Creutzfeldt-Jakob disease to chimpanzees by intracerebral inoculation of infected brain, both of these diseases were classified as "degenerative" abiotrophies of the nervous system.

To date, the chemical nature of the scrapie agent remains obscure. The unusual physio-chemical properties of the scrapie agent and its slow replication in the absence of any detection by host defense mechanism suggest that scrapie is a novel infectious entity. Unlike viruses, the scrapie agent cannot be visualized by electron microscopy and its presence does not provide a detectable immunological response.

This research program is directed in part toward understanding the "slow" nature of the scrapie agent. Because the present assay for scrapie requires determination of an endpoint by titration in mice over nine months, an effort is directed to the search for the partial purification of the scrapie agent, as well as the use of this preparation to explore chemical and immunological assay systems. The purification and subsequent elucidation of the chemical structure of the scrapie agent promises to bring new concepts and techniques to several areas of molecular biology and medicine.

Because of the extensive background knowledge concerning viral infections, the anatomy, physiology, chemistry and pharmacology of the Peripheral Autonomic Nervous System (PANS), the use of autonomic ganglia to study infection of neural tissue with HSV presents a unique opportunity. These ganglia are readily manipulated surgically or pharmacologically, their metabolic and functional profile can be followed with well characterized biochemical markers, and their in vitro cultivation has reached an advanced state of sophistication. The results of such studies might be applied to other neural cell populations just as studies of development of these ganglia, of their neuronal circuitry and of their synaptic chemistry have been used as models of different and more complex neural structures.

One of the goals, relevant to MS and ALS research, is to define the pathogenesis of latent and reactivated herpes simplex virus infection of the peripheral autonomic nervous system. Among the aspects of this infection to be studied are: (a) the factors leading to acquisition of autonomic infection, (b) the determinants of latency, (c) the cellular changes responsible for viral reactivation, (d) the neural and target organ sequelae of reactivation, and (e) whether latent infection of autonomic ganglia occurs in man. Three complementary approaches are used by a NINCDS grantee to achieve the proposed objective: (1) studies employing a murine model of in vivo infection of the superior cervical ganglion of the sympathetic division of the autonomic nervous system, (2) studies employing an in vitro model of latent and reactivated HSV infection to be developed using dissociated cell cultures derived from autonomic ganglia, and (3) explantation of human autonomic ganglia obtained at the time of postmortem examination.

These studies are undertaken because of their direct importance to human diseases, because infection with HSV serves as a paradigm of viral infection of the autonomic nervous system, and because they open a new approach to studying infection of the nervous system with this virus.

Studies on viral persistence in lymphocytic choriomeningitis virus have been carried on by investigators at the Scripps Clinic and Research Foundation and on measles virus and variants by investigators in San Francisco and at Ann Arbor. The studies of VISNA virus being carried on in collaboration in San Francisco and at Johns Hopkins show quite clearly that VISNA is incorporated into the genome of the host cell and that somehow the expression of this virus is blocked. VISNA is capable of rather rapid change or mutation within the host, and at different stages of development within the host animal, the virus is producing different kinds of protein.

The sheep, despite the fact that they have an appropriate acute cell-mediated immune response, become sick and progress in relapsing and remitting phases to death. The investigators hypothesize that this progression of neurological disease in the face of attempts by the host to defend itself may represent the cumulative effect of clinically apparent attacks induced by intermittent release of antigenically altered virus. Thus, the phenomena of lysogeny, the technical term for incorporation of the viral genome into the host genome, and antigenic drift may combine to provide a unique mechanism which explains the acute episodes of relapsing and relapsing disease. In addition to human diseases mentioned, this kind of mechanism has been proposed for multiple sclerosis, for subacute panencephalitis, and certain forms of senile dementia.

It is a tribute to the advance in antibiotic therapy that the categories dealing with infections in the classical sense, encephalitis and meningitis, have become less troublesome in recent years. However, bacterial meningitis has increased in the United States during the past several years and in particular, a striking increase in infection due to Hemophilus influenzae type b has been observed. Most recently, an increased incidence of meningitis due to group B beta hemolytic streptococci in children over one month of age but less than six months of age has been observed. The following are the first prospective studies of bacterial meningitis performed in the antibiotic era. At Baylor College of Medicine to date, 235 patients have been enrolled. These studies have documented for the first time that prior treatment with antibiotics should not preclude making a specific etiologic diagnosis of meningitis provided a complete evaluation of cerebrospinal fluid, blood and urine is performed utilizing countercurrent immuno-electrophoresis in addition to the usual morphologic and chemical evaluation of cerebrospinal fluid.

These studies have shown that the mortality rate to less than 2 percent in patients followed with great care can be reduced. They have also documented that severe sequelae of bacterial meningitis such as hemi- or quadriplegia (noted in 30 of 235 children at the time of discharge) may

disappear with time. At discharge, abnormal neurological findings may be present in up to 35 percent of patients, but by two years after discharge neurologic deficits were found in only 7.1 percent of the total group. These findings illustrate that even severe neurologic deficits that are noted in children who have recovered from bacterial meningitis may improve with time. Since all previous studies have been retrospective, observations of this type were not possible previously. Detailed psychological testing has revealed IQ scores in the group of patients who were enrolled which were not significantly different from a sibling control group. Thus, these studies have also documented that profound mental retardation is not a very common concomitant of bacterial meningitis when the disease occurs in children over one month of age.

The studies also have demonstrated by specific measurement of anti-diuretic hormone by radioimmunoassay (the first time that this has been done in patients with infection of the central nervous system) that an inappropriate secretion of antidiuretic hormone occurs commonly in patients with bacterial meningitis and is treated best by fluid restriction.

Specific assessment of the development of polyribosephosphate (PRP) antibody directed against Hemophilus influenzae type b antigen demonstrated that children less than 17 months of age generally did not develop this type of antibody response irrespective of the antigenic stimulus to which they were exposed by their natural disease.

The ability of the serum of young children to opsonize (prepare for ingestion by polymorphonuclear leukocytes) Hemophilus influenzae type b is significantly less than normal adult sera as assessed by a special technique known as chemiluminescence. In addition, there is no increase in opsonic activity from acute to convalescent sera obtained from children with meningitis due to Hemophilus influenzae type b. These data correlated with the lack of anti-PRP antibody production emphasize the need for vigorous continuing research efforts in the evaluation of the normal host response to H. influenzae infection. Unless these differences between the host response in young children and older children or adults to Hemophilus influenzae type b infection can be understood, the hope of developing a vaccine for the prevention of this disease will not be realized.

In conclusion, these prospective studies have demonstrated that appropriate early and vigorous treatment of the patient with bacterial meningitis can limit both neurologic and psychometric sequelae of the disease. The studies also have demonstrated the requirement for very careful control of fluid balance as an important adjunct to the therapy of patients with bacterial meningitis. They have demonstrated the utility of countercurrent immunoelectrophoresis as a routine procedure for establishing the rapid etiologic diagnosis of this disease. They also have demonstrated dramatic deficits in host response in children less than 17 months of age referable to both humoral antibody and polymorphonuclear leukocyte function.



ANNUAL REPORT

October 1, 1978 through September 30, 1979

Epilepsy Branch, NDP
National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
October 1, 1978--September 30, 1979

Epilepsy Branch
Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health

A milestone event in the Epilepsy Branch occurred on July 1, 1979, when its founder, J. Kiffin Penry, M.D., retired as a Commissioned Officer in the U.S. Public Health Service. Dr. Penry served as Chief of NINCDS epilepsy program since his appointment as Chief, Section on Epilepsy, July 1, 1966. Since that time, the Branch has grown to be a world leader in epilepsy affairs; clinical treatment of patients with seizures; antiepileptic drug development; comprehensive epilepsy programs; and controlled trials of antiepileptic drugs--critical clinical data was provided from studies which were included in the New Drug Applications for carbamazepine, clonazepam, and valproic acid. Another important aspect of the program has been the dissemination of scientific information about epilepsy. The Epilepsy Branch will miss the direction of Dr. Penry; the Acting Chief will be Roger J. Porter, M.D.

The Epilepsy Branch conducts both extramural and intramural programs from three locations of the National Institutes of Health. Extramural activities are housed in the Federal Building which is the principal location of the Branch. The pharmacology laboratory is in Building 36, and clinical epilepsy research is in Building 10. The latter program is conducted in cooperation with the Experimental Therapeutics Branch, Intramural Research Program. The Federal Building continues to be a major source of problems since the General Services Administration appears unable to control the environment of the video and computer laboratory--heat and humidity controls are required for video and audio tape stability. NIH has undertaken a vigorous attempt to improve control and maintenance. It remains to be seen, however, if this attempt will be successful.

A year and a half has elapsed since the introduction of valproic acid as an antiepileptic drug in the United States. There has been wide acceptance of this drug by physicians. Valproic acid is considered a significant advance in the treatment of seizures. The President of Abbott Laboratories has estimated first year sales at \$10 million, about 20% of the antiepileptic drug market. The availability of valproic acid in the United States expands the opportunity for its continued investigation. There is still a great deal to be known about this drug; its utility in some seizure types remains to be determined, and questions about its metabolism and mechanism of action must be clarified. Likewise, the mechanism of hepatic toxicity requires investigation. Other research will be concerned with diurnal serum fluctuations of valproic acid in relation to seizure control. The efficacy of the drug employed as a single drug therapy in various seizure types is of great interest since most studies have employed combination drug treatments. To further knowledge of valproic acid, NINCDS Bibliography No. 3, Valproic Acid, a Classified Bibliography with Keyword and Author Index was issued this year and widely distributed. Two studies employing this drug have been completed and are undergoing analysis. The first of these is a study in absence seizures conducted at the University of Virginia; the second employed valproic

acid in the treatment of generalized tonic-clonic seizures at New Castle State Hospital, Indiana. Each of these studies will provide important information about the utility and safety of valproic acid.

Partial support for the clinical epilepsy research program is provided by the Experimental Therapeutics Branch, IRP, NINCDS, while the major portion of personnel and funding is provided by the Epilepsy Branch. The clinical epilepsy section studies improved seizure control, reduction of drug-induced side effects, and improved potential for rehabilitation through the utilization of newly developed intensive monitoring techniques. These include simultaneous video recording of seizures, long-term telemetered EEGs, and daily serum antiepileptic drug determinations. Particular efforts were directed towards intensive monitoring of the psychogenic seizure and its differentiation from other seizures. In 78 patients monitored intensively, six were diagnosed unequivocally as psychogenic seizure patients. A single antiepileptic drug was used for the first time in patients considered to have intractable complex partial seizures. Perhaps not surprisingly, preliminary findings in 9 patients suggest that most patients with intractable seizures are more effectively treated with a multiple drug regimen than with phenytoin alone. The training of neurologists in treatment of epilepsy is an important function of this section. A clinical associate served during the one year. Beginning the next fiscal year, a Nigerian neurologist will serve as an international fellow in epilepsy at a World Health Organization neuroscience center in the epilepsy section. A second international fellow is scheduled for 1980.

The Anticonvulsant Drug Development program is the cornerstone of Epilepsy Branch programs. Although small in comparison to many at NIH, this program is concerned with all aspects of drug development from synthesis of new compounds to their clinical evaluation and ultimate marketing by the pharmaceutical industry. The screening program for anticonvulsant activity of new chemicals conducted by the University of Utah has been expanded to include an evaluation of protection against chemical convulsants by new compounds. This discrimination shows differences among marketed anticonvulsants which are believed to predict similarities and differences among new agents and highlight new agents offering different mechanisms of action from traditional drugs. Of the several thousand compounds screened, about 40 are being followed closely. Meetings have been held with officials of two pharmaceutical companies to discuss developing their drugs. It is expected that a contract will be awarded late in the fiscal year to provide toxicologic evaluation of the most promising agents screened. This is a new factor in the anticonvulsant drug development program which will further encourage industry towards the development of new drugs. Eleven grants were awarded for the synthesis of novel compounds in response to a request for grant applications issued by NINCDS; these chemists will supply compounds to the screening program for evaluation. There are several drugs in clinical development as antiepileptic agents. The Branch is working closely with one U.S. manufacturer to provide advice about clinical evaluation. Another drug which the Branch is interested in arises from a Japanese pharmaceutical company. Informal discussions have been undertaken with a U.S. company regarding exploration of an indication for the treatment of seizures for a drug already under investigation for another purpose.

As President of the International League Against Epilepsy and Chairman of the Executive Committee, Epilepsy International, J. Kiffin Penry, M.D., has worked to organize and support international symposiums on epilepsy. Very successful international meetings were held in September 1978 in Vancouver, British Columbia, and September 1979 in Florence, Italy. They demonstrated a high level of interest and achievement in epilepsy research throughout the world. There were four themes in Florence: Anatomical, electrical and clinical manifestations of human and experimental epilepsy; the neurobiological basis of epilepsy; advances in drug treatment; and psychosocial problems of people with epilepsy.

More than 50 visitors concerned with epilepsy visited the Epilepsy Branch; many of these were from foreign countries. Their visits provided the opportunity to discuss their involvement in detail with members of the Epilepsy Branch staff. Of particular interest to many visitors was the intensive monitoring of patients, using telemetered electroencephalograms and video in the Clinical Center. Other individuals found the pharmacology laboratory of extreme relevance to their own study of the metabolism of antiepileptic drugs. Visitors are welcomed so that they may adapt our techniques to their own situation, thus fostering the transfer of technology from the National Institutes of Health to practicing physicians and universities.

Since the Commission for the Control of Epilepsy and its Consequences submitted its recommendations to Congress in 1977, the Institute continues to monitor the progress of agencies responsible for the conduct of recommendations, and to act upon recommendations affecting NINCDS. Progress has been made with a number of recommendations in both areas. Epilepsy Branch staff collaborates with the Epilepsy Foundation of America by participating in its task force on implementation of the Commission's plan.

Five Comprehensive Epilepsy Programs are supported by the Institute. The first three, the University of Minnesota, The Good Samaritan Hospital Medical Center, Portland, Oregon, and the University of Virginia are in their fifth and final year. A decision has been made by the Institute to provide the opportunity for further funding of the major clinical research portion of the programs through the research grant mechanisms; the minor coordinating function may be supported through research contract. Two programs are in their fourth year, the Medical College of Georgia, and the University of Washington. The latter two were subjected to technical merit review by an ad hoc expert committee at the end of their third year, and funding for an additional two years was recommended in each instance. Following recommendations from the Epilepsy Advisory Committee and the Commission for the Control of Epilepsy and its Consequences, the Institute solicited research proposals for an urban comprehensive epilepsy program. Owing to an administrative restriction that only labor surplus areas could respond, only five locations were eligible for this contract. Several of the eligible cities were represented by research proposals; they were reviewed by an ad hoc technical merit review committee late in the fiscal year. It is anticipated that an award will be made early in FY80.

Another important aspect of the Epilepsy Branch services is the provision of scientific information about epilepsy. The Institute supports the

publication Epilepsy Abstracts, a monthly abstracting service provided by the Excerpta Medica Foundation. A computer tape from this contract is provided to the National Library of Medicine so that a data retrieval system, EPILEPSYLINE, is available to users of MEDLINE or TOXLINE. Within the Epilepsy Branch an information system has been developed as a collection of more than 36,000 references comprising most of the current scientific literature and pertinent historical documents. Using computer assisted techniques, three epilepsy indexes were printed, each containing 10,000 citations. These citations were made available worldwide during the year to facilitate reference to the epilepsy literature.

On June 19, 1979, J. Kiffin Penry, M.D., testified before the House Committee on Research and Technology concerning the U.S. regulation of drugs. This Committee was concerned with the so-called "drug lag" and requested information about the development and marketing of valproic acid. The hearings pointed out the need for changes in the drug law to accelerate the marketing of therapeutic advances and provide the opportunity to market drugs of little commercial value.

The Epilepsy Branch pharmacology laboratory was fortunate to have a postdoctoral fellow during the year who is an expert in the use of high-pressure liquid-chromatography in connection with drug metabolism. The drug-drug interaction of valproic acid and phenobarbital was investigated in the Clinical Center in patients with epilepsy using mass-spectrometry and liquid and gas chromatography. The study has been completed in two patients, and the results presented at the annual meeting of the American Society for Pharmacology and Experimental Therapeutics. It was shown that the mechanism for the increase in phenobarbital concentrations caused by valproate suggests that a primary effect is at the site of metabolism of phenobarbital with inhibition of hydroxylation rather than by increased renal absorption or changes in the volume of distribution. Consultation was provided to a number of individuals wishing to establish a laboratory for serum concentration determination of drugs.

The Branch has provided consultation for a quality control program for laboratories performing determinations of serum concentrations. Since July 1, 1979, the program has been sponsored by the American Association of Clinical Chemists. Two voluntary directories of laboratories adequately performing serum concentrations were issued, one in January and the other in June 1979. The directories were sponsored by the American Epilepsy Society and funded by the Institute. The directory answers a need of physicians and patients who need to know laboratories which accurately and reliably determine antiepileptic drug concentrations.

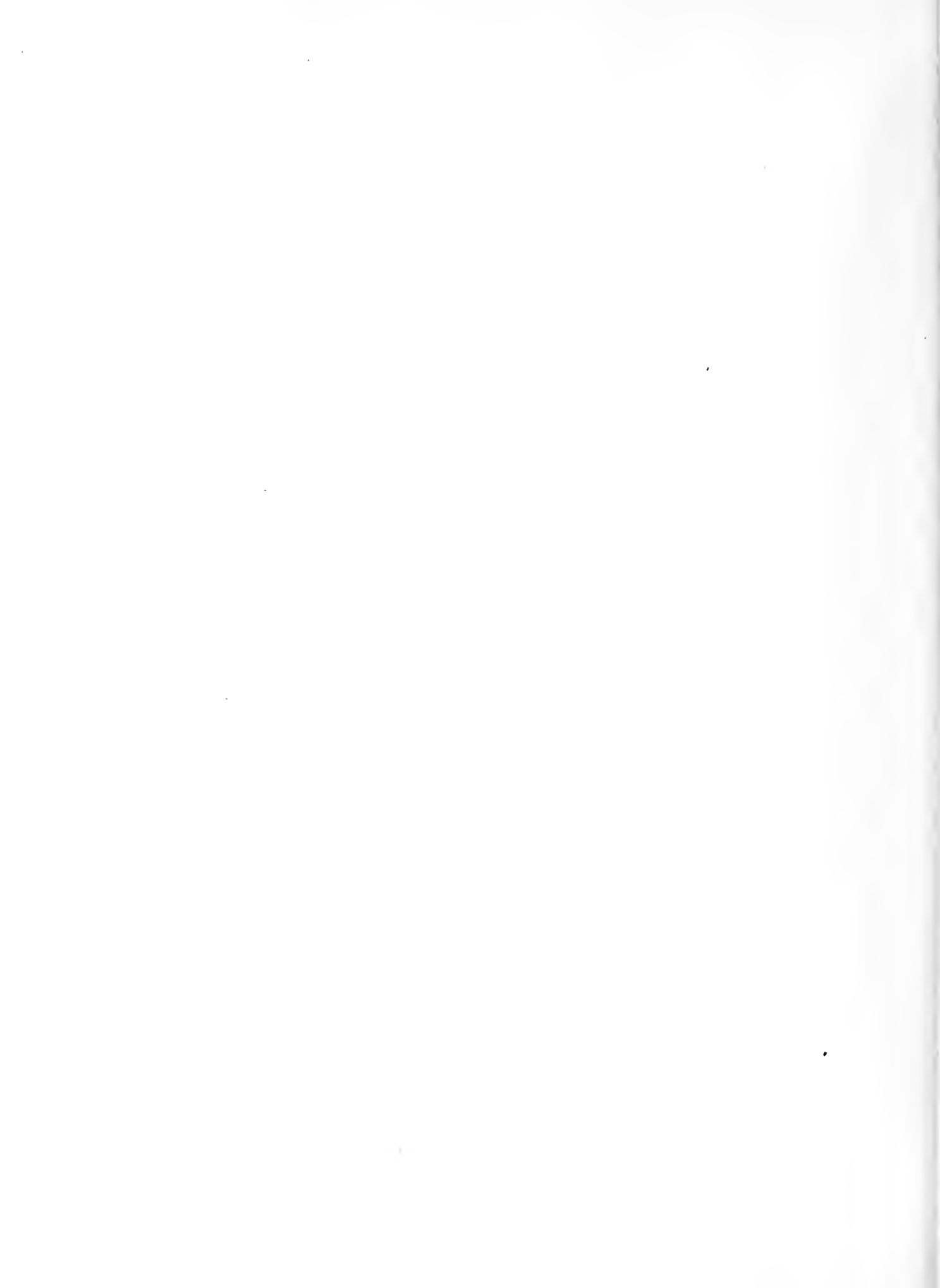
Throughout the country, there is a high degree of interest in seizure disorders and their treatment. The senior professional staff contribute to the education of physicians and other professionals through numerous lectures and continuing education programs. One of these was unique in that it used a communication satellite for distribution of the program from the University of South Carolina. A second educational film sponsored by Geigy Laboratories has been produced in response to the excellent reception received by the first film, Complex Partial Seizures. The

sequel is on the differential diagnosis of complex partial seizures and consists of portions contributed by professional staff of the Epilepsy Branch, and a senior investigator of the University of Virginia.

Following recommendations of the Commission for the Control of Epilepsy and its Consequences, the Institute plans to sponsor two grant supported workshops, one on the genetics of epilepsy, and the other on the treatment of status epilepticus. Grant applications have been received for funding in FY80.

Since 1972, the Branch has sponsored a research contract to investigate the pharmacologic prophylaxis of posttraumatic epilepsy. The study was designed to determine if a minimal dose of phenytoin and phenobarbital could prevent the occurrence of seizures after head injury. A double-blind study conducted at the University of Kansas in 125 patients showed no significant difference; half were treated with drugs and half with placebo for 18 months. These findings were presented to the American Academy of Neurology in April, 1979. Because serum concentration of drugs was very low, due to the minimal dose used, a second study was undertaken in which therapeutic serum concentrations are employed. While accession of patients to the study has been slow, there are preliminary indications that results will differ from the previous study.

In response to recommendation of the Epilepsy Advisory Committee, a study was undertaken at the University of Houston to quantify infantile spasms and use prednisone in a pilot treatment study. The study successfully showed that it is possible to quantify infantile spasms in an accurate manner. A decision was made to conduct a controlled study of drugs in this disorder and a Sources Sought announcement was issued to determine the capabilities of investigators in this country. A request for research contract proposal was issued and resulted in an award late in the fiscal year. While the incidence of this disorder is low, its consequences are severe and a difficult therapeutic problem for the physician. For this reason, results of this study will be of great practical importance.



CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

NEW CASTLE STATE HOSPITAL (N01-NS-68-1310)

Title: Development of a Model for Assessment of New Anticonvulsant Agents

Contractor's Project Director: John Van Meter (Acting)

Current Annual Level: \$10,000

Objectives: To further develop models to study the efficacy, safety and bio-availability of new antiepileptic drugs in humans. The most recent investigation included study of the antiepileptic property of sodium valproate when substituted for phenobarbital in the therapy of patients with generalized seizures refractory to treatment, the evaluation of possible side effects of the drug, and evaluation of drug serum concentrations.

Course of Contract: The study of sodium valproate was completed in the fall of 1977. Clinical data was sent to the Epilepsy Branch, NINCDS, Bethesda, for review and preparation for computer aided analysis. Final verification and analysis of the data is underway.

Major Findings: Preliminary analysis of data appears to indicate that sodium valproate may be substituted for phenobarbital in the therapy of patients with generalized seizures.

Significance to NINCDS Program and Biomedical Research: The pharmaceutical industry had demonstrated little interest in developing new antiepileptic agents. Aside from the economic factors involved, one of the industry's major problems is to obtain satisfactory clinical studies of antiepileptic drugs. Through this contract and others, NINCDS has supported clinical studies of antiepileptic drugs. Well controlled studies--as conducted at New Castle State Hospital--will be significant indicators of therapeutic merit of new antiepileptic drugs and may encourage the pharmaceutical industry to develop promising agents for clinical trial. It is anticipated NINCDS-sponsored studies will enable drugs to reach the market more readily, and thus be available to physicians who treat patients with seizures.

Proposed Course of Contract: Evaluations of other investigational antiepileptic drugs and further development of the model for drug evaluation are pending.

Publications: None.

C.T. No. 0700761

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE (N01-NS-9-2196)

Title: Absence Seizure Drug Studies

Contractor's Project Director: Fritz E. Dreifuss, M.D.

Current Annual Level: \$60,000

Objectives: To evaluate the effectiveness of valproic acid and of ethosuximide on the frequency and intensity of absence (petit mal) seizures in patients previously untreated for this disease, and in patients who have failed to be controlled by ethosuximide; to evaluate drug effects on physiologic and other functions.

Course of Contract: A pilot study preceded the present controlled study of 47 patients. Twenty-five of these were in phase one where maximum valproic acid dose was 30 mg/kg, and 22 in phase two where the maximum is 60 mg/kg.

Major Findings: Long-term EEG telemetry and video recording were used as the primary measure of efficacy for evaluating treatment differences during this clinical trial. During period one of the study, seizures were completely controlled in six (85.7%) of the 7 naive patients who received VPA (valproic acid), and in 4 (44.4%) of 9 naive patients treated with ethosuximide. Although this difference is not statistically significant, p greater than 0.05, it does suggest that VPA is more efficacious than ethosuximide in reducing generalized spike-wave bursts on telemetered EEG. When analyzing results from both period one and two of the study, 37.5% of the naive patients had a 100% reduction in seizure frequency on VPA, but not on ethosuximide, and 12.5% on ethosuximide, but not on VPA. Because 37.5% of the naive patients responded to either VPA or ethosuximide, the overall response was 75% to VPA and 50% to ethosuximide. This difference is not statistically significant, but suggests that for naive patients that VPA is more efficacious than ethosuximide in reducing generalized spike-wave bursts on telemetered EEG. In refractory patients, a similar finding was produced although again not statistically significant. No patients dropped out of the study because of side effects which were generally mild and responded to dosage reduction of VPA.

Proposed Course: The final results of this absence seizure study are in press. A follow-up of patients entered into the absence drug studies is also being conducted to determine long-term drug effects.

C.T. No. 0700759

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

UNIVERSITY OF WASHINGTON (N01-NS-0-2281)

Title: Complex Partial Seizure Drug Studies

Contractor's Project Director: Alan J. Wilensky, M.D., Ph.D.

Current Annual Level: \$200,000

Objectives: To compare the relative antiepileptic efficacy and safety of clorazepate dipotassium and phenobarbital in patients receiving phenytoin for partial seizures; to measure drug concentrations in patients' blood; and to assess patients' psychological competence.

Course of Contract: Fifty-six patients entered the double-blind controlled study, providing 43 patients with complete data.

Major Findings: This study design is similar to previously conducted controlled drug trials with other drugs. Preliminary results indicate that clorazepate is as effective as phenobarbital as an adjunct to phenytoin. Some of the neuropsychological tests appear to favor clorazepate. Clorazepate, a benzodiazepine drug, was well tolerated as an antiepileptic drug. Significantly, more subjects preferred the combination of clorazepate and phenytoin to phenobarbital and phenytoin. This preference is based upon the patient's degree of seizure control and side effects of the treatment. Since the incidence of seizures was essentially the same for both treatments in most patients, it was concluded that clorazepate has about the same antiepileptic activity as phenobarbital. Subjective side effects were greater with phenobarbital than with clorazepate.

Proposed Course: This contract has been completed. Future controlled drug studies in patients with complex partial seizures will be conducted in connection with the University of Washington Comprehensive Epilepsy Program contract, N01-NS-6-2341.

Publications:

Dodril CB, Wilkus RJ: Neuropsychological correlates of the electroencephalogram in epileptics: III. Generalized nonepileptiform abnormalities. Epilepsia 19:453-462, 1978.

Dodril CB: A neuropsychological battery for epilepsy. Epilepsia 19: 611-623, 1978.

Wilensky AJ, Levy RH, Troupin AS, Ojemann LM, Friel P: Clorazepate kinetics in treated epileptics. Clin Pharmacol Ther 24:22-30, 1978.

Troupin AS, Friel P, Wilensky AJ, Ojemann RM, Levy RH, Feigl P: Evaluation of clorazepate (Tranxene^R) as an anticonvulsant--A pilot study. Neurology (Minneap) 29: April, 1979.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

UNIVERSITY OF WASHINGTON (N01-NS-1-2282)

Title: Study of Experimental Antiepileptic Drugs in Animals

Contractor's Project Director: Joan S. Lockard, Ph.D.

Current Annual Level: \$514,000

Objectives: To compare the antiepileptic efficacy of drugs in primates with spontaneous motor seizures. Seizure frequency and behavioral toxicity are compared with drug dosage and drug blood concentration. Metabolic and pharmacokinetic studies are conducted.

Course of Contract: Since this anticonvulsant drug research contract in the primate was awarded competitively in June, 1971, it has been highly effective and productive. The first 18 months were devoted to the development of validation of the primate model of focal seizures. A series of quantitative drug evaluations were then performed. These studies were efficacy of anticonvulsants, documentation of the role of social factors in drug therapy, single dose pharmacokinetic experiments, long-term studies, and mass-spectrometry of metabolites of anticonvulsant drugs.

Major Findings: The methodology was determined for the simultaneous analysis of carbamazepine and the epoxide by gas chromatography mass-spectroscopy stable isotope methodology. Then, the pharmacokinetics of carbamazepine-10, 11-epoxide before and after autoinduction were studied. An efficacy study was conducted to evaluate carbamazepine under constant rate intravenous infusion in 8 epileptic monkeys. The attenuation of seizures by carbamazepine was not statistically significant as the serum levels of carbamazepine after enzyme induction were less than 2 ug/ml. Carbamazepine induced both its metabolism and that of its 10-11 epoxide. Diurnal oscillations in carbamazepine serum concentrations were also evident.

The pharmacokinetics of the 7-amino metabolite of clonazepam was investigated. In monkeys, this metabolite has a larger total body clearance, a smaller volume of distribution, and a shorter half-life than the parent drug. The nitroreduction pathway represents an important route of elimination of clonazepam. The efficacy of clonazepam was then investigated. Because of its insolubility and short half-life, a constant rate intravenous infusion method was employed to achieve a plasma level of 30 and 60 ng/ml. The results indicated that clonazepam is effective for focal motor and secondarily generalized tonic-clonic seizures, particularly at the higher concentration. Withdrawal seizures were evident when the drug was stopped.

A one step gas liquid chromatography procedure was developed for the quantitative determination of valproic acid in plasma. After addition

of internal standard, plasma is buffered and evaporation avoided. The method was found to be precise and reproducible. Cinromide (3-bromo-N-ethylcinnamamide) was evaluated in epileptic monkeys. Three steady state plasma levels were achieved. Cinromide was found to be effective in the model at a plasma concentration range of 7-14 ug/ml of the active metabolite, 3-bromocinnamamide. Six animals were employed, and only one developed secondarily generalized seizures during drug administration. Minimal side effects were shown, but withdrawal seizures were observed. Further evaluation of this drug is underway.

Because of world politics, the supply of *Macaca mulatta* is unreliable. For this reason, another primate, *Macaca fascicularis*, was studied to determine its suitability as a substitute model for experimental epilepsy. Chronic recurring seizures developed following aluminum hydroxide injection as readily as the present animal. Comparable drug plasma levels and seizure frequency patterns were observed. There are small differences between the two species in diet, tail length, and body size. Major readjustments in housing and maintenance will not be required. Thus, *Macaca fascicularis* was determined to be an alternative should it be necessary to abandon *Macaca mulatta*.

A study was conducted on the influence of attending (scheduled feeding periods, visual attending, and three different operant tests) on seizure activity in epileptic monkeys. The data suggests that when the monkey is attending to an operant task, there is an attenuation of EEG and neuronal epileptic activity as well as a decreased probability of ictal events. However, monkeys with a high frequency of paroxysms have a paradoxical effect in that attending may increase ictal or interictal EEG or single unit epileptiform activity. Attending or participation in the operant task results in a decrease in the burst behavior of neurons and a disruption of synchrony between pacemaker and normal neurons.

This lowers the probability of an ictal event occurring either during or immediately following operant task. Depending on the neuronal composition of the focus attending to an operant task may either attenuate or augment epileptiform activity. Thus, it was concluded that keeping the brain engaged in non-epileptic behavior may exclude its employment in epileptic activity.

Proposed Course: Studies will continue on the pharmacokinetic, metabolic, and efficacy of antiepileptic drugs as this is the only chronic model of seizures for focal motor and secondarily generalized tonic-clonic seizures. It has been proven valid on a genetic basis, and empirically evaluated and found that antiepileptic drugs efficacious in man in gross motor seizures are also efficacious in this model. Drugs specific to other seizure types are not efficacious. An ingenious constant rate infusion system for administration of drugs via a femoral catheter has been developed along with chronic sampling for drug concentrations via a jugular catheter. Drugs of long biologic half-life but insoluble may be administered orally on a chronic basis using a nasogastric tube. Drugs of short half-life may be administered using a gastric duodenal cannula for constant infusion. Using an implanted EEG plug, continuous frequent

electroencephalographic sampling is possible without disturbing the monkeys. Quantification of epileptiform activity as sleep staging is routinely ascertained using an intraventricular catheter and reservoir system. This model will soon be capable of performing chronic sampling of cerebrospinal fluid.

This model also provides the ability to perform extensive behavioral assessment of drug effects, such as reaction time, judgment, toxicity, psychotropic or sedative effects in restrained animals and in the free roaming room. Computerized techniques provide data from these assessments. Also, this model is suitable for drug interaction and drug tolerance and withdrawal studies. Precision pharmacokinetic and metabolic studies are also possible. Likewise, the proximity of this research within the Department of Neurological Surgery provides short-term spectral analysis of EEG, single neuron, and histologic studies associated with the anticonvulsant drug studies.

Publications:

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Lai AA, Levy RH, Cutler RE. Time-course of interaction between carbamazepine and clonazepam in normal man. Clin Pharmacol Ther, 24:316-23, 1978.

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Lockard JS, Levy RH, Congdon WC, DuCharme LL. Efficacy and toxicity of the solvent polyethylene glycol 400 in monkey model. Epilepsia 20:77-84, 1979.

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Lockard JS, Ojemann GA, Congdon WC, DuCharme LL. Cerebellar stimulation in alumina-gel monkey model - inverse relationship between clinical seizures and EEG interictal bursts. Epilepsia, 20:223-234, 1979.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

UNIVERSITY OF KANSAS MEDICAL CENTER (N01-NS-2-2313)

Title: Investigation of Pharmacologic Posttraumatic Epilepsy Prophylaxis

Contractor's Project Director: Charles Brackett, M.D.

Current Annual Level: \$100,000

Objectives: A study to determine the effectiveness of therapeutic treatment with phenytoin and phenobarbital in persons who suffer severe head injury and are thus liable to posttraumatic epilepsy. This study was preceded by a pilot study with prophylactic doses in less severely injured patients.

Course of Contract: One hundred and twenty-five patients were accessioned in the pilot study, and all have completed the required 18-month treatment, and the remaining eligible patients were also followed for another 18-month period of no drug treatment. Eleven patients experienced seizures while on the study, and four had seizures after completion of drug therapy. Results of this pilot study are currently in preparation for publication. The continuation of the study in severely injured patients with therapeutic doses of phenobarbital and phenytoin has admitted 41 patients as of 7/16/79. Seventeen have completed the 12 months of drug treatment, and three of these patients have completed the entire 18 months of study. Seven patients have experienced seizures as of 7/16/79.

Proposed Course of Contract: The overall results of the pilot study will be published. Also, there will be additional investigation into the relationship between study drug doses and plasma levels. The current study utilizing therapeutic dosages will accession sufficient patients so that statistically valid inferences can be made regarding the prevention of posttraumatic seizures. It is anticipated that if current trends continue, no more than 50 patients will be admitted.

C.T. No. 0700757

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

EXCERPTA MEDICA FOUNDATION (N01-NS-3-2303)

Title: Publication of Epilepsy Abstracts, Volume 11

Contractor's Project Director: Pierre Vinken, M.D.

Current Annual Level: \$50,000

Objectives: To scan serial publications and periodicals from approximately 3500 world biomedical journals and select appropriate articles to be included in Epilepsy Abstracts in accordance with the guidance of the Project Officer and his editorial advisors; prepare abstracts with appropriate translations into English from foreign languages; classify, index, and store the abstracts in a computer retrievable form; and produce a 9-track, 1600 bpi computer tape for use at NIH. The text is automatically set by computer-operated photocomposition. The Excerpta Medica Foundation produces camera-ready copy for each monthly issue of Epilepsy Abstracts, which includes an index of subjects and authors and prints, and distributes the journal monthly with a cumulative index at the end of the volume. In order to pay for the production of the camera-ready copy, printing, and distribution, the Excerpta Medica Foundation sells subscriptions to recover these costs.

Course of Contract: Subscriptions to Epilepsy Abstracts, each at annual cost of \$69.25, have been acquired from interested persons by Excerpta Medica at a satisfactory rate. Interest in the publication continues at a high level throughout the world.

Proposed Course of Contract: Continued publication of monthly issues of Epilepsy Abstracts; computer tapes delivered to NIH bimonthly in accordance with the contract. These tapes comprise the EPILEPSYLINE data base retrievable throughout the country via MEDLINE or TOXLINE terminals.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

STANFORD RESEARCH INSTITUTE (N01-NS-3-2322)

Title: Continuous Development of a Wearable Eight-Channel EEG Cassette Recording System

Contractor's Project Director: Charles S. Weaver, Ph.D.

Current Annual Level of Funding: \$11,000

Objectives: The objective of this project is to fabricate, maintain and evaluate a wearable EEG recording system; to design and fabricate an economical playback system without computer tape format; and to design a data compression scheme. This development includes a hybridized amplifier system to provide for eight-channels of differential recording connected to a wearable tape recorder with appropriate signal processing electronics. Digital encoding circuitry provides for a full dynamic range and suitable bandwidth to allow for automatic processing of EEG data by computer. In addition to the design and development of the recording technique and implementation in hardware, the overall system is to be clinically evaluated with a selected group of patients under environmental conditions similar to those in which it will ultimately be used. The playback system is to transcribe the encoded data from initial tape cassettes and reform the original analog EEG on a strip chart through micro-processor, as well as to interface to a computer.

Major Findings: The first eight-channel recorder and playback system was delivered on December 3, 1976. Now, two on-body systems with hybridized amplifiers are in use. The system weighs approximately five pounds and records eight-leads of EEG for twelve hours on a standard C-120 audio cassette with a bandwidth of 40Hz. The system successfully underwent engineering evaluation and was accepted in March 1977. It is now undergoing extensive clinical evaluation at the Clinical Center, NIH, and elsewhere. Reliability and reproducibility have been tremendously improved by improved wiring in the headpiece and modification of digital circuits in the playback system. Planning is well underway for transfer of this new technology to allow commercial production of the recording system.

Significance to Biomedical Research and the Program of the Institute: The availability of a lightweight high-fidelity portable EEG tape recorder will allow significant improvement in both diagnosis and therapy of some types of epilepsy, and provide numerous research opportunities, e.g., evaluation of drug treatment of seizures.

Proposed Course of the Contract: Field evaluation will continue after contract expiration this fiscal year.

Collaborating Units: This project is being carried out as a collaborative effort of the Neurological Disorders Program and the Fundamental Neurosciences Program. The Neurological Disorders Program is providing the clinical direction and the funding, while the Fundamental Neurosciences Program is providing the technical direction and project management.

Publications:

Sato S, Penry JK and Burch JD. Eight-channel digital recorder for monitoring partial and generalized seizures. ISAM 1977, p93-104, Eds. F. D. Stott, et al. Academic Press, 1978.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

UNIVERSITY OF UTAH (N01-NS-5-2302)

Title: Initial Pharmacologic Development of New Drugs

Contractor's Project Director: Ewart A. Swinyard, Ph.D.

Current Annual Level: \$335,000

Objective: To determine the anticonvulsant properties of novel organic compounds at various levels of testing from preliminary screening to extensive activity and toxicity profiles.

Course of Contract: Compounds are received by NINCDS from academic and industrial medicinal chemists and sent to the University of Utah for testing. Initially, the levels of anticonvulsant and neurotoxicity activities are determined on all compounds submitted. For those compounds which exhibit anticonvulsant activity without signs of neurological deficit, the ED50 and TD50 are determined. The pharmacologic data is then provided to NINCDS where it is reviewed and analyzed. The submitters of compounds are then informed of the results and any proposed additional testing, which may be warranted. Those compounds which are selected as the most promising are scheduled for advanced testing (Phases III-VII). The advanced phases of testing incorporate the oral route of administration (all preceding testing performed intraperitoneally) using the mouse and rat along with a complete toxicity profile and drug characterization of doses at 1, 2, and 4 times the TD50 on the compound given intraperitoneally in mice. Recently included in the advanced phases of testing is an antiepileptic drug differentiation testing whereby 4 chemically induced seizure models are used to predict possible modes of action as compared to the currently marketed antiepileptic drugs. Another recent addition to the advanced testing is a LD50 determination in rat p.o.

Proposed Course of Contract: This program began January 1, 1975 and during the period October 1, 1978 through September 30, 1979 screened 685 compounds for anticonvulsant activity. Currently, 54 compounds have been scheduled for the advanced phases of testing with 12 compounds completing all of these phases.

Publications:

1. Swinyard EA and Woodhead JH. Drug Contamination of Mortar and Pestles. J. Pharm. Sci., 67:1758-1759, 1978.
2. Krall RL, Penry JK, Kupferberg HJ, and Swinyard EA. Antiepileptic Drug Development: I. History and a Program for Progress. Epilepsia, 19:393-408, 1978.

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CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

Contractor		Project Director	Annual Level
Univ of Minnesota	(N01-NS-5-2327)	R. Gummit, M.D.	\$2,188,419
Good Samaritan Hosp Portland	(N01-NS-5-2328)	J. Schimschock, M.D.	990,521
Univ Va Med Center	(N01-NS-5-2329)	F. Dreifuss, M.D.	1,120,788
Med Coll Georgia	(N01-NS-6-2340)	J. Green, M.D.	602,682
Univ of Washington	(N01-NS-6-2341)	A. Ward, Jr., M.D.	984,022

Title: Comprehensive Epilepsy Program

Objectives: The objective of the Comprehensive Epilepsy Program is to facilitate applied research and to coordinate research and teaching with health care services related to persons with all types of epileptic seizures within a defined geographic area.

Courses of Contracts: Each contractor is conducting clinical and laboratory research in the diagnosis, treatment, prognosis and prevention of epilepsy. Each contractor is demonstrating to physicians and other professionals the newest advances in epilepsy research and treatment and is establishing a broad program for public education. In addition, each contractor is establishing the required procedures to assure, in a research setting, the availability to the person with epilepsy of complete and up-to-date preventive medical and rehabilitative psychological, vocational, educational, and social services.

Major Findings: During fiscal year 1975 three Comprehensive Epilepsy Programs were established. During fiscal year 1976 two additional programs were established. All of the contractors showed evidence for the feasibility of establishing a program in their geographic area by a detailed description of clinical research capability, health care delivery, rehabilitation, resources, etc., for the person with epilepsy. All of the programs underwent Technical Merit Review prior to beginning of the fourth year.

Proposed Course: During the coming year, the Comprehensive Epilepsy Programs will facilitate applied research and coordinate research and teaching with health care services related to persons with all types of epileptic seizures within their defined geographic area. Inpatient facilities will be made available to patients for periods of 3-6 months to receive special diagnostic evaluation and intensive treatment of their seizure disorders and any other concurrent handicap or physical problem. Vocational training, psychological support, other ancillary services and continued schooling will be simultaneously provided. Existing services will be coordinated for maximum utilization. An integral part of the program will be demonstration at all levels in the management of patients with epilepsy for professionals, para-professionals, and the lay public. While it is recognized that care for persons with epilepsy is available from many sources at the present time, these are scattered and noninclusive so that a patient may or may not receive total care depending on the local resources and how well they are coordinated.

Publications:

University of Minnesota:

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CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1978--September 30, 1979

METHODIST HOSPITAL-HOUSTON (N01-NS-6-2342)

Title: Quantification and Treatment of Infantile Spasms

Contractor's Project Director: Peter Kellaway, Ph.D.

Current Annual Level: \$5,400

Objective: To develop a quantitative clinical methodology to describe infantile spasms; and to conduct a pilot evaluation of their treatment with prednisone.

Course of Contract: The first portion of this contract has been completed, and an effective time synchronized monitoring system for the study of patients with infantile spasms was developed. This system utilizes concurrent graphically recorded data including electroencephalogram, body movement via accelerometry, respiration, electrocardiogram, electromyogram, electrooculogram, and galvanic skin response. Closed circuit television recordings are made of the patients and evaluated to facilitate the differentiation of seizures from non-ictal activity. This permits the characterization and quantification of the behavioral, motor, and autonomic phenomenon intrinsically associated with infantile spasms. The second part of the study, to conduct a pilot study of prednisone in patients with infantile spasms using the methodology developed for quantification, has also been completed. A film on the differential diagnosis, manifestations, and treatment of infantile spasms was produced. It will be owned and distributed by the Government for the education of physicians and other health professionals.

Proposed Course: This contract has been completed. Because it has been found practical to quantify infantile spasms, the Institute will issue a Request for Proposals to obtain a controlled clinical trial of drugs using these methodologies. A contract award is anticipated late in the fiscal year.

Publications:

Kellaway P, Hrachovy RA, Frost JD, Zion T: Precise characterization and quantification of infantile spasms. Ann Neurol, (in press) 1979.

Hrachovy RA, Kellaway P, Frost JD, Zion T: A controlled study of prednisone in infantile spasms. Epilepsia, (in press) 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01933 09 EB						
PERIOD COVERED October 1, 1978 to September 30, 1979								
TITLE OF PROJECT (80 characters or less) Quantitation of Spike-Wave Activity by a Reaction Time Method								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: J. K. Penry</td> <td style="width: 33%;">Chief, Epilepsy Branch</td> <td style="width: 33%;">EB, NDP, NINCDS</td> </tr> <tr> <td>Others: S. Sato</td> <td>Visiting Scientist.</td> <td>EB, NDP, NINCDS</td> </tr> </table>			PI: J. K. Penry	Chief, Epilepsy Branch	EB, NDP, NINCDS	Others: S. Sato	Visiting Scientist.	EB, NDP, NINCDS
PI: J. K. Penry	Chief, Epilepsy Branch	EB, NDP, NINCDS						
Others: S. Sato	Visiting Scientist.	EB, NDP, NINCDS						
COOPERATING UNITS (if any) F. E. Dreifuss, M.D., Professor of Neurology Department of Neurology University of Virginia								
LAB/BRANCH Epilepsy								
SECTION								
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, MD 20205								
TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1						
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) This study determines whether reaction time in <u>absence</u> patients is or is not impaired in a gradual fashion from the point of spike-wave initiation. A <u>reaction-time</u> device is employed which gives instantaneous recognition by voltage criteria that a spike-wave burst has started. This burst is of much higher than normal background, and this factor alone is used to electronically trigger the reaction timer. On instantaneous recognition the reaction timer is triggered and a tone is delivered to the subject. The subject responds by turning off the high pitch tone with a telegraph key. Between paroxysms the patient is maintained in a state of alertness.								

Project Description:

Objectives: To determine whether reaction time in patients with absence (petit mal) seizures is or is not impaired in a gradual fashion from the point of spike-wave initiation as has been suggested by some authority but disputed by others. There is some evidence for a "trough-like" pattern decrease of consciousness. The onset of decreased clinical functions during spike-wave paroxysms is evaluated by the reaction time method.

Methodology: A device is employed which gives instantaneous recognition by voltage criteria that a spike-wave burst has started. This burst is of much higher than normal background, and this factor alone is used to electronically trigger the reaction timer. On instantaneous recognition the reaction timer is triggered and a tone is delivered to the subject. The subject responds by turning off the high pitch tone with a telegraph key. Between paroxysms the patient is maintained in a state of alertness by a program of approximately 10 random stimuli per minute. All the data is collected by television, including a portion of the screen reserved for the reaction time from the digital clock. There is no age limit in selecting patients, but they must all have spike-wave paroxysmal discharge. A second group of patients was studied with the apparatus altered slightly so that the auditory stimulus was delivered 0.5 seconds into the seizure in order to see if responsiveness becomes less as the seizure progresses. Oscillographic displays from magnetic tape recordings of spike-wave paroxysms revealed shifting asymmetries.

Major Findings: The first group of patients suggests that some ability to respond early during the paroxysmal burst is maintained; this responsiveness is frequently not seen 1-2 seconds after onset. Analysis of responsiveness during short bursts suggests that patients may retain a normal reaction time during such paroxysms.

Significance: This study has applied video recording techniques and sophisticated electronic methods to improve the quality of clinical research. Specifically, this study is an analysis of the relation of the patient's behavior to his EEG during paroxysmal electroencephalographic events. An understanding of this relationship is important--not only as a guidepost for further research in the mechanism of epilepsy, but also in determining the day-to-day therapeutics of the epileptic patient.

Future Course: This project will continue. Patients from an investigational drug study will be evaluated.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02097 08 EB						
PERIOD COVERED October 1, 1978 to September 30, 1979								
TITLE OF PROJECT (80 characters or less) Diagnostic Value of Prolonged Telemetered EEG in Epilepsy								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%;"> <tr> <td style="width: 33%;">PI: J. K. Penry</td> <td style="width: 33%;">Chief, Epilepsy Branch</td> <td style="width: 33%;">EB, NDP, NINCDS</td> </tr> <tr> <td>Others: S. Sato</td> <td>Visiting Scientist</td> <td>EB, NDP, NINCDS</td> </tr> </table>			PI: J. K. Penry	Chief, Epilepsy Branch	EB, NDP, NINCDS	Others: S. Sato	Visiting Scientist	EB, NDP, NINCDS
PI: J. K. Penry	Chief, Epilepsy Branch	EB, NDP, NINCDS						
Others: S. Sato	Visiting Scientist	EB, NDP, NINCDS						
COOPERATING UNITS (if any) W. L. Brannon, M.D., Chief Neurology Service U.S. Naval Medical Center, Bethesda, MD 20014								
LAB BRANCH Epilepsy								
SECTION								
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, MD. 20205								
TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1						
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) Telemetered EEGs are recorded for 6 hours in order to sample over a longer period of time than the usual 20-30 minutes, and during normal activity. The incidence of diagnostic paroxysmal abnormalities in the 6-hour telemetered EEG are compared with those from routine conventional EEGs. About 10% of patients have had diagnostic abnormalities on the 6-hour telemetered EEG which were not recorded in the routine EEG. The ability to detect and record diagnostic epileptiform abnormalities in the EEG after a single seizure will aid in the early treatment and long-term prognosis of patients who suffer their initial seizure.								

Project Description:

Objectives: To develop a means of detecting and recording interictal paroxysmal abnormalities (epileptiform) in the EEG of patients who have suffered a clinical convulsion.

Methodology: Telemetered EEGs are recorded for 6 hours in order to sample over a period of time longer than the usual 20-30 minutes and during normal activity; in some patients, the latter may evoke interictal paroxysmal abnormalities in the 6-hour telemetered EEG with those from routine conventional EEGs. One hundred patients have been evaluated.

Major Findings: In the initial group of patients studied, about 10% have had diagnostic abnormalities on the 6-hour telemetered EEG which were not recorded in the routine EEG. The accessioning of patients has been completed and the results will be analyzed and published in the near future.

Significance: If patients could be detected before the occurrence of a seizure, they could be treated and the seizure prevented, without treating those patients who will not have a recurrence.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02334 02 EB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) The Relationship of Pentylenetetrazole (Metrazol) Brain Levels to Seizure Activity in Mouse Brain		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: H. J. Kupferberg Pharmacologist EB NDP NINCDS Others: W. Yonekawa Pharmacologist EB NDP NINCDS		
COOPERATING UNITS (if any) D. Woodbury, M.D., Professor Department of Pharmacology University of Utah		
LAB/BRANCH Epilepsy		
SECTION		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Pentylenetetrazole (PTZ) when administered subcutaneously to mice causes various types of <u>seizure</u> activity. First observed is myoclonic jerks, followed by clonic seizures and finally by clonic running and generalized tonic extension seizures. With low doses the initial seizures only are observed. By increasing the dose, the entire seizure complex occurs. The convulsive dose ₅₀ needed to induce clonic seizures in mice without inducing tonic hindlimb extension was found to be 60 mg/kg. The CD ₅₀ of PTZ needed to induce the entire seizure complex was found to be 95 mg/kg. Brain concentrations of PTZ were measured by gas liquid chromatography following the administration of 60 mg/kg and 95 mg/kg at the time of clonic seizures and tonic hindlimb extension, and were found to be 53 ug/gm and 79 ug/gm respectively. There appears to be a relationship between the amount of PTZ in the brain and the severity of seizures induced by PTZ.		

29 - EB/NDP

Project Description:

Objectives: To determine whether there exists a relationship between mouse brain levels of pentylenetetrazole (PTZ) and the severity of seizures.

Major Findings: The CD_{50} for pentylenetetrazole-induced clonic seizures was 60 mg/kg and the brain level of PTZ at the time of clonic seizure was 53 μ g/gm. The CD_{50} for PTZ induced maximal tonic hindlimb extension seizures was 95 mg/kg and the brain level at the time of tonic seizure was 79 μ g/gm. There is a direct relationship between brain levels of PTZ and the seizure type.

Significance: This provides insight into the understanding of the mechanism of action of chemically induced seizures.

Proposed Course: This project has been completed.

Publications:

Yonekawa W, Kupferberg HJ, Woodbury DM: Relationship between pentylene-tetrazole-induced seizures and brain and plasma PTZ levels in mice. Abstract #620, Pharmacologist, 21, 1979.

ANNUAL REPORT

October 1, 1978 through September 30, 1979

Developmental Neurology Branch, NDP
National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
For Period October 1, 1978 through September 30, 1979
Developmental Neurology Branch, Neurological Disorders Program
National Institute of Neurological and Communicative
Disorders and Stroke
National Institutes of Health

GENERAL SUMMARY

I. INTRODUCTION:

The objective of the Developmental Neurology Branch (DNB) is to develop and implement a program of research on the neurobiological aspects of the developmental disorders of children including cerebral palsy and other motor disorders, autism and behavioral disorders, mental retardation and learning disorders, and central nervous system birth defects and genetic disorders. Near the end of the last fiscal year the DNB was formally reorganized and new sections were established which corresponded to the four subprogram areas. Prior to the reorganization the DNB's single responsibility was to direct the NINCDS Collaborative Perinatal Project (NCPP). A fifth section of the DNB serves as the data bank for computer tape and microfilm files of the NCPP. A major effort during this fiscal year has been to complete the objectives of the Comprehensive Plan for Analysis and Interpretation of Collaborative Perinatal Project Data.

II. NINCDS COLLABORATIVE PERINATAL PROJECT:

The NINCDS Collaborative Perinatal Project (NCPP) is a longitudinal multidisciplinary research effort which seeks leads to the etiologies of cerebral palsy, mental retardation, learning disorders, congenital malformations, minimal brain dysfunction, convulsive disorders, visual abnormality, and communicative disorders through studies which relate the events, conditions, and abnormalities of pregnancy, labor and delivery to the neurological and mental status of the children of these pregnancies as the child grows and develops. Data collection has been completed, and data analysis is now complete in most areas of study. The Comprehensive Plan for Analysis and Interpretation of Collaborative Perinatal Project Data provided the framework for this effort. The Comprehensive Plan includes 10 primary and 10 secondary areas of study as listed below. The major emphasis of the project has shifted almost entirely to data interpretation and the writing of reports for publication of the NCPP research findings. Significant publications stemming from the Comprehensive Plan are noted in the listing below if the study area is completed, in the individual contract narratives or project reports, and some are highlighted in the General Summary.

A. The ten primary areas are:

Cerebral Palsy (Project No. Z01 NS 02059-07 DNB)

Mental Retardation (Project No. Z01 NS 02106-06 DNB)

Communicative Disorders (See Contract No. N01-NS-4-2326)

Visual Abnormality (Project No. Z01 NS 02107-06 DNB)
Convulsive Disorders (Project Nos. Z01 NS 02058-07 DNB
Z01 NS 02234-04 DNB)
Learning Disorders (Project No. Z01 NS 02108-06 DNB)
Minimal Brain Dysfunction (Project No. Z01 NS 02062-07 DNB)
Congenital Malformations (Project No. Z01 NS 02109-06 DNB)
Birthweight-Gestational Age Relationships (Project No.
Z01 NS 02060-07 DNB)
Neuropathology, General Pathology and Placentology (Contract Nos.
N01-NS-3-2312 & N01-NS-7-2376)

B. The ten secondary areas are:

Toxemia (Completed in FY'77 - See Friedman, E.A., and Neff, R.K.: Pregnancy Hypertension. Littleton, Mass., PSG Publishing Co., Inc., 1977, 258 pp.)

Maternal Infection during Pregnancy (See report by Infectious Diseases Branch, NINCDS)

Neonatal Hyperbilirubinemia (Project No. Z01-NS-02112-06 DNB)

Maternal Anesthesia-analgesia during Labor and Delivery (Contract No. N01-NS-8-2381, and Project No. Z01 NS 02169-05 DNB)

Four-Year IQ (Completed in FY'75 - See Broman, S.H., Nichols, P.L., and Kennedy, W.A.: Preschool I.Q.: Prenatal and Early Developmental Correlates. Hillsdale, N.J., Lawrence Erlbaum Associates (distributor, Halsted Press, John Wiley & Sons, N. Y.) 1975, 360 pp.

Physical Growth and Development (Contract No. N01-NS-5-2308)

Twins (Project Nos. Z01 NS 02109-06 DNB and Z01 NS 02332-02 DNB)

Genetic and Socio-economic Factors (Project Nos. Z01 NS 01514-13 DNB, Z01 NS 01857-10 DNB, Z01 NS 01754-11 DNB, and Z01 NS 01274-15 DNB)

Drugs taken during Pregnancy (Completed in FY'77 - See Heinonen, O.P., Slone, D., and Shapiro, S: Birth Defects and Drugs in Pregnancy. Littleton, Mass., Publishing Sciences Group, Inc., 1977, 516 pp.)

Labor and Delivery (Contract No. N01-NS-8-2381)

III. SUMMARY OF WORK IN PROGRESS:

Reflecting the reorganization of the Developmental Neurology Branch, this segment of the annual report is organized to indicate the respective contributions of the new Sections.

Section on Cerebral Palsy and Other Motor Disorders

In the cerebral palsy area a univariate screen has been reevaluating maternal and pediatric conditions most strongly associated with cerebral palsy. Initial regression analyses have been run. Cerebral palsy at 7 years is found more frequently in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma. Clearly handicapping cerebral palsy was present at age 7 in 22-33/10,000 children, the range being related to race and sex. Studies have been completed demonstrating the relationship of birth-weight and gestational age to cerebral palsy. Within each birthweight and gestational age group examined white males were at highest risk of cerebral palsy. Although low birthweight and immaturity are risk factors for cerebral palsy, 59% of cerebral palsy and 69% of the cerebral palsy other than spastic diplegia occurred in infants of term weight and full (37 or more weeks) gestational age. Studies are now in progress concerning low Apgar scores at 10, 15, and 20 minutes as predictors of long-term neurological morbidity, early recognition of infants at "high-risk" for cerebral palsy, associated handicaps in children with cerebral palsy, and of children who "outgrew" cerebral palsy, i.e., those children who showed signs of cerebral palsy at an earlier age but at the 7-year examination were free of motor handicap.

In the convulsive disorders area, major findings are that approximately one in 20 children [57/1000] at age seven years have had at least one seizure. About 1/10 of that number [4.8/1000] had active epilepsy by the age of seven. In the NCPP population active epilepsy in childhood is slightly more common in girls than in boys and approximately equal in rate in blacks and whites. Data on prevalence of specific seizure disorders in early childhood are now available and a manuscript is in preparation on this subject. Other findings of importance are that approximately a quarter of the children with epilepsy in early childhood have another major neurological handicap--either mental retardation or cerebral palsy, or both. It is also noted that seizures occurring in the first months of life were associated with a relatively high rate of death or subsequent disability including cerebral palsy. Neonatal seizures were found to be a major marker of risk for subsequent neurological morbidity.

A study of febrile seizures has been a major focus of the convulsive disorders area. Of 1821 children with febrile seizures in the NCPP population, 1706 were followed to the age of 7 years. Two per cent had become epileptic by the age of 7 and another 1% had had at least one febrile seizure not meeting the definition of epilepsy. Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ or increased vulnerability to learning disorders. There were no deaths and no acquired motor defects associated with febrile seizures in this series. Current activities on febrile seizures include a proposed NIH consensus meeting on the management of children with febrile seizures.

Section on Mental Retardation and Learning Disorders

In the mental retardation area, epidemiological findings show that the incidence of severe retardation at seven years does not differ by ethnic group, but mild retardation was more frequent among blacks than whites. The incidence of mild retardation, and to a lesser extent, severe retardation, decreased as social class increased. Major neurological problems were more frequent among whites than blacks in both retarded groups. Within an ethnic group, the proportion of retarded children with neurological abnormalities increased with social class. Identified risk factors for mental retardation include urinary tract infections during pregnancy, teen-age pregnancy, clinical signs of perinatal anoxia, and poor psychomotor performance in infancy. A monograph is in preparation.

In the learning disorders area, low achievers (children with average IQ scores and below-average achievement test scores) were born into large families of lower socioeconomic status as compared with IQ-matched controls. More than two-thirds of the group were boys. As preschoolers, they had difficulties with verbal tasks and relatively low IQ scores. At age 7, signs of deviant behavior, verbal and non-verbal cognitive deficits, and neurological soft signs were present. Mothers of hyperactive low achievers had an increased frequency of obstetrical complications. A monograph is in preparation.

In the area of minimal brain dysfunction, significant associations were found between major symptoms (learning difficulties, hyperkinetic-impulsive behavior, and neurological "soft signs") and many socioeconomic, perinatal, developmental, and familial variables. Although the antecedent variables identified were not efficient predictors, they differed significantly between normal and affected groups and are therefore of potential etiological significance. To study long-term outcomes, there are current plans to follow some of the affected children through adolescence. The manuscript of a book has been completed and is undergoing review prior to publication.

Work also continued by the Section concerning obstetric anesthesia-analgesia and infant and child development. Analysis of a cohort of normal births followed through the first year of life indicates that infants of women given inhalant anesthetics had increased frequencies of palpable liver and spleen, and deficits in motor development as compared with infants of women given regional anesthesia. Relationships between obstetrical medication and later physical and cognitive development in this cohort are also being analyzed.

Section on Birth Defects and Genetic Disorders

Only two parts of the 11-part program plan for the comprehensive analysis of congenital malformations remain to be completed: the analysis of multiple malformations, which has been initiated, and the analysis of the 7-year malformations which is now in progress. Preliminary findings from the latter analysis indicate that about 19% of children followed to age 7 years have malformations, representing an increase of 4% from 1 year, which is mainly due to newly identified eye, mouth, and genito-

urinary malformations, and tumors. In-depth studies of microcephaly and pyloric stenosis have been initiated. The performance of an in-depth study of congenital heart defects has been added to the responsibilities of this Section. The study is now in progress.

The objective of the twins project is to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of NCPP twins.

Section on Autism and Behavioral Disorders

Studies have continued on the 14 autistic children identified in the NCPP. Earlier published work on this sample reported increased vaginal bleeding during the second trimester of pregnancy. Cord blood samples have been examined for presence of certain antiviral antibodies but no significant results were found. Analysis of the placentas for abnormalities is underway. Tabulations have been prepared on the autistic children and controls for a series of findings from the neonatal neurological examination, the 8-month developmental examination, and the 1-year neurological examination in an attempt to identify predictive signs of autism.

Proceedings of the Workshop on the Neurobiological Basis of Autism have been published as NINCDS Monograph No. 23. The volume reports on the presentations and discussions of the following topics: definition, neuropsychology, language, neurophysiology (vestibular and evoked potential research), and neurochemistry. A recruitment effort for the Section Head for the Autism and Behavioral Disorders Section continues.

Collaborative Perinatal Section

The monograph in the area of communicative disorders, a project which was completed under contract, underwent extensive editing by DNB staff. All tables, figures and other graphic art work (653 pages) were reviewed and edited by staff following termination of the contract. The book Early Correlates of Speech, Language and Hearing is in press.

In the area of visual abnormality data analyses were completed this fiscal year and a monograph reporting results is in preparation.

The Birthweight-Gestational Age Relationships (Prematurity) analyses, including graphs and tables of Phases I and II, have been completed. The examination of a Birthweight Index to determine its predictive value for birthweight-gestational age outcomes has been completed. Writing of the text of the monograph is underway.

Studies in the area of pathology continued under two separate contracts, one for neuropathology and one for general and placental pathology. In the neuropathology segment, work on the manuscript of the monograph report continued during the fiscal year, and completion is expected in the fall of 1979. An extensive chapter will report on myelination of the fetal brain. Other chapters will report on focal necrosis and

intracranial hemorrhage. The general and placental pathology contract has resulted in numerous publications. Among the most recent are reports on causes of perinatal mortality in the NINCDS Collaborative Perinatal Project; amniotic fluid infections with intact membranes leading to perinatal death; predisposing factors and effects on the fetus and surviving infants of placenta previa; causes and consequences of placental growth retardation; causes of perinatal mortality excess in prolonged gestations; causes of perinatal death associated with gestational hypertension and proteinuria; underlying disorders of neonatal apnea; amniotic fluid infections, neonatal hyperbilirubinemia, and psychomotor impairment; and effects of maternal cigarette smoking on the fetus and placenta.

The contracted study of toxemia of pregnancy is complete and a book published. Friedman, E.A. and Neff, R.K.: Pregnancy Hypertension. Littleton, Mass., PSG Publishing Company, Inc., 1977, 258 pp.

A book describing the characteristics of NCPP children during their first year has been published. Hardy, J., Drage, J.S., and Jackson, E.: The First Year of Life. Baltimore, Md., The Johns Hopkins University Press, 1979, 327 pp.

Studies on neonatal hyperbilirubinemia have suggested that neurological impairment at one year may be associated with neonatal serum bilirubin levels below 20 mg.%. During the current year, an analysis of neonatal bilirubin levels and seven year outcomes has been completed. Data are being interpreted and readied for publication.

Work has continued under contract on the Comprehensive Study of Labor and Delivery Effects on Offspring. The contractor has determined labor incremental durations, assessed progression patterns, defined distributions of dilatation and descent parameters, quantified outcome effects of these labor variables, identified dysfunctional labors, and investigated outcome effects of disordered labor patterns.

Work in the area of physical growth continued this fiscal year and the contract was extended, without additional funds, in order to complete work already planned and to complete the reporting of results. A monograph is in preparation.

The contracted screening study of maternal drug ingestion is complete and a book published. Heinonen, O.P., Slone, D., and Shapiro, S.: Birth Defects and Drugs in Pregnancy. Littleton, Mass., Publishing Sciences Group, Inc., 1977, 516 pp.

IV. HIGHLIGHTS OF FINDINGS FROM THE NCPP

Findings from the NCPP have had and are continuing to have an impact on national health policy. It seems appropriate to highlight some of the more important contributions to date.

The concern over the potential dangers of alcohol consumption by a pregnant woman to her unborn fetus was highlighted in a notice in

the Federal Register, Vol. 44, No. 29 - Friday, February 9, 1979. In that notice, the Department of the Treasury recommended a public awareness campaign to educate the public about the nature of the problem. The existence of the "fetal alcohol syndrome," a constellation of congenital anomalies thought to appear in offspring of chronic alcoholic women, was confirmed, prospectively, using data on women and children enrolled in the NCPP. The appearance of the paper in the Lancet (Jones, K.L., Smith, D.W., Streissguth, A.P., and Myrianthopoulos, N.C.: Outcome in offspring of chronic alcoholic women. Lancet I: 1076-1078, 1974) stimulated additional research and subsequent governmental and public concern over this issue.

The work by Dr. Dennis Slone and his colleagues at Boston University, completed under contract with the NINCDS, developed an association between cardiovascular birth defects and female hormones taken by the mother during pregnancy. The paper appearing in the New England Journal of Medicine (Heinonen, O.P., Slone, D., Monson, R.R., Hook, E.B., and Shapiro, S.: Cardiovascular birth defects and antenatal exposure to female sex hormones. N. Engl. J. Med. 296: 67-70, 1977) led directly to new Federal drug labeling requirements for this class of drugs as published in the Federal Register, Vol. 43, No. 199 on Friday, October 19, 1978. The paper is cited in the Federal Register.

Febrile seizures affect 3.5 percent of all children born in the United States. The study by Drs. Karin Nelson and Jonas Ellenberg, of the NINCDS, (Nelson, K.B and Ellenberg, J.H.: Prognosis in children with febrile seizures. Pediatrics 61: 720-727, 1978) presented data concerning the degree of risk of future epilepsy in children experiencing febrile seizures. In children with a prior neurological abnormality and one or more other risk factors (family history of epilepsy, first seizure type), the risk was high, but for children with no prior abnormality, no history of epilepsy in the immediate family, and when the first seizure was of a pure (not complex) type, the risk of subsequent epilepsy was quite low. This low risk group included 60% of children with febrile seizures and the authors state that this group would not seem an appropriate target population for chronic treatment aimed at the prevention of afebrile seizures. Another 34% of children had only one risk factor and they experienced little increase in risk of epilepsy. The NINCDS is planning a Consensus Meeting which will attempt to resolve the issue of management of febrile seizures in current medical practice.

In 1979 a report of the Surgeon General on Smoking and Health was released. Chapter 8 is on Pregnancy and Infant Health and there are six references to publications from the NCPP that significantly contribute to the report's conclusion that smoking during pregnancy is deleterious to the baby during intrauterine life.

Other significant findings from the NCPP include evidence that there is prior neonatal brain dysfunction in sudden infant death syndrome (Naeye, R.L., Ladis, B., and Drage, J.S.: Sudden infant death syndrome: a prospective study. Am. J. Dis. Child. 130: 1207-1210, 1976), that only one third of congenital malformations are detected at birth (Myriantho-

poulos, N.C. and Chung, C.S.: Congenital malformations in singletons. Epidemiologic survey. Report from the Collaborative Perinatal Project. Birth Defects, Orig. Art. Series, Vol. X, No. 11, 1974), and that bilirubin is neurotoxic at intermediate levels (Scheidt, P.C., Mellits, E.D., Hardy, J.B., Drage, J.S., and Boggs, T.R.: Toxicity to bilirubin in neonates: infant development during the first year in relation to maximum neonatal serum bilirubin concentration. J. Pediatr. 91: 212-297, 1977.)

V. CONTRACT DEVELOPMENT:

No new contracts were awarded this fiscal year. Planning for a number of new initiatives was begun and new contract plans are being drafted.

VI. SUPPORT FUNCTIONS:

The Unit for Data Collection is responsible for maintaining the NINCDS Collaborative Project files and the microfilming of the records in accordance with a system designed to facilitate data retrieval. During the fiscal year major efforts were concentrated on preparation of records for microfilming, editing microfilm, supplying records to the DNB professional staff, outside investigators and consultants, and providing research assistance for ongoing studies.

The Unit for Production of Data Analysis has as its basic mission the processing and storage by digital computer of the medical research data collected by the NCPP. The Unit provides data processing support to the researchers in their analysis of the data. The major research files have been completed and in-depth statistical analysis is being performed. By the end of the fiscal year, approximately 30 requests for analysis will have been completed. The following automated systems are in operation: (1) A financial system that accounts for all computer funds spent by the Unit or programming contractor; and (2) A follow-up job system that monitors all active jobs. The following systems are being created or are under study: (1) An automated bibliography of all publications emanating from the NCPP; (2) An index of all variables found in the Master-File, Variable File and Peripheral Files; and (3) A tape documentation system that will describe and define all tapes created and stored by DNB.

VII. OUTSIDE REQUESTS FOR NCPP DATA:

It is the policy of the DNB to encourage the appropriate use of the NCPP data by providing advice, data, and assistance to qualified biomedical and behavioral researchers who wish to utilize these data in their research. A policy statement has been developed which specifies the requirements to be met by a researcher who wishes to utilize NCPP data supplied by the DNB. The policy statement was formally approved by the Director, NINCDS and is available on request.

Requests for NCPP data to initiate new studies or to obtain specific information from NCPP data files continue to be received from research-

ers who receive their support from agencies and institutions other than the NINCDS. New requests this fiscal year include:

University of Washington, Seattle, on the evaluation of transillumination as a screening test in the newborn period; Schering Chemicals Ltd. (West Sussex, England) on birth defects in children of mothers receiving sex hormones during the first 4 lunar months of pregnancy; Godding Division, St. Elizabeth's Hospital, Washington, D.C., on the effects of the use of hexachlorophene on the newborn; University of Missouri Medical Center, Columbia, on the epidemiology of premature labor; School of Health Sciences, University of Massachusetts, Amherst, on the reproductive outcome and occupational histories of mothers and fathers; Division of Child Psychiatry, College of Physicians and Surgeons, Columbia University, New York, on neuropsychological profiles of NCPP children; Department of Pediatrics, UCLA School of Medicine, on the risk factors of prolonged rupture of membranes to infants; Division of Gastroenterology, The Children's Hospital Medical Center, Boston, on the incidence of Hirschsprung's disease; Chronic Disease Division, Center for Disease Control, Atlanta, Georgia, on parity and maternal age incidence of Rh hemolytic disease of the newborn; School of Public Health, Columbia University, New York, on the etiology of Down's Syndrome.

VIII. ADDITIONAL ACTIVITIES:

The Office of the Chief, DNB, continues as the NINCDS focal point for the Privacy Act. The Chief, DNB, continues to serve as NINCDS Privacy Act Coordinator. Activities for this fiscal year include the following: (1) advice to NINCDS personnel regarding Privacy matters; (2) determination of the applicability of the Privacy Act to each new NINCDS contract involving human subjects; (3) required quarterly and annual reports prepared and submitted to the NIH Privacy Act Coordinator; (4) reviewing requests for access to or amendment of grant records; and (5) impact of the Privacy Act on peer review and other NIH functions.

The Office of the Chief, DNB, continues to administer the NINCDS Clinical Research Panel for extramural contracts and the Chief, DNB, serves as Chairman. This panel has the responsibility for reviewing NINCDS contracts for adherence to DHEW and NIH rules and regulations regarding the protection of human subjects in research and recommending approval or disapproval to the Director, NINCDS. During the first nine months of the fiscal year, 18 new contract proposals were reviewed by the Panel, and 33 renewals were processed.

The Chief, DNB, and the Staff Assistant to the Chief, DNB, are members of the NIH Contract Compliance Committee for Project Officers, chaired by the Contract Compliance Coordinator, NIH. This committee has as its charge the development of a questionnaire to be administered by project officers to principal investigators/project directors on NIH contracts for the purpose of increasing awareness of and monitoring compliance with Federal requirements for Equal Employment Opportunity. During this fiscal year a questionnaire was finalized by the Committee and approved by the Collaborative Program Directors, NIH. The next stage is implementation via formal training sessions for NIH Project Officers.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1978 through September 30, 1979

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS (N01-NS-3-2312).

Title: Combined Neuropathologic and Epidemiologic Study

Contractor's Project Director: Floyd H. Gilles, M.D.

Current Annual Level: \$ 0.00

Objectives: The contract will analyze the neuropathology collection of the NINCDS Collaborative Perinatal Project (NCPP). An estimate of the quality of the material and a catalogue of gross brain abnormalities will be prepared. Plots of fetal brain weight of grossly normal brains against estimated gestational age, utilizing a Gompertz function, will be made and an analysis will be made relating events of pregnancy, labor, and delivery. A comparison will be made of rate of brain weight acquisition in utero to rate of brain weight acquisition after birth as a function of total (gestational plus survival) age. A study will be made of intracranial hemorrhage including topography of hemorrhage. A study will be done on the risk factors associated with perinatal telencephalic leucoencephalopathy. A study of cerebral necrosis is to be completed which would include criteria of necrosis in the perinatal brain, and an evaluation of selected risk factors in relation to subclassification of neuronal and white matter necrosis.

Major Findings: Review and classification of pathology material are complete. Data analysis is complete and a monograph report is expected during the fiscal year.

Course of Contract: June 1, 1973 through December 31, 1976. The contract is terminated; extra time is being allowed to complete and publish the monograph report.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1978 through September 30, 1979

UNIVERSITY OF MINNESOTA (N01-NS-4-2326)

Title: Analysis of Speech, Language and Hearing Deficits to Facilitate Prevention, Diagnosis and Treatment

Contractor's Project Directors: Frank M. Lassman, Ph.D., and
Robert O. Fisch, M.D.

Current Annual Level: None

Objectives: Speech, language and hearing (SLH) data were collected as part of the Collaborative Perinatal Project (NCPD) of the National Institute of Neurological and Communicative Disorders and Stroke. Clinical populations and a group of private patients were sampled at twelve medical institutions located largely in eastern and southern states. Data from SLH examinations administered at 3YR and 8YR were analyzed for interrelationships and for associations with findings in other areas of the NCPD study. These include variables relating to pregnancy, labor and delivery, family characteristics and the physical, mental and behavioral characteristics of the children. Relationships among the variables were studied to provide clues to the etiology of communicative disorders, and to uncover findings which might be clinically applicable as well as predictive of outcome.

The SLH data were examined for quality as it pertains to availability of the data, reasonableness of values and stability of findings. Examiner variability was evaluated on the basis of test-retest results obtained from the NCPD quality control program. The quality of most SLH variables appeared satisfactory in general.

Major Findings: Two multiple regression analyses were performed using the 3YR SLH indexes as outcomes. One used data at birth, and the other used at-birth plus 8-month mental and motor scores. In general, these predictors explained less than 8% of the variance. The better predictions were for 3YR Articulation, Intelligibility, Language Comprehension and Sentence Complexity.

Five multiple regression analyses were done using the 8YR indexes as outcomes. In addition to the two sets of predictor variables used for 3YR outcome, the 4YR IQ and 3YR indexes were used in various combinations. Best predictions occurred for 8YR Word Identification, Concept Development, Written Communication, Language Production, Language Comprehension, Auditory Memory and Articulation.

In brief, relationships between SLH outcome and selected NCPD variables included the following: 1. Race, sex, SEI and IQ contributed most to predicting the 8YR language indexes; 2. Failure on 8-month Bayley vocalization items increased by 2 to 3 times the risk of later poor language performance; 3. Single children performed better than those with siblings;

4. Written communication (reading, writing, spelling) showed systematic improvement with increasing IQ, SEI and education of the parents; 5. Failure of the 3YR Pure Tone Hearing Screen was predictive of loss in hearing sensitivity at 8YR; 6. Higher relative risks for sensorineural hearing loss in children was suggested for certain drugs administered to mothers during pregnancy; and 7. Variables indicative of socioeconomic level have the strongest relationship to SLH outcome at 8YR.

Course of Contract: June 29, 1974 through June 28, 1976. Extension of time was required for completion, but with no additional funding. Contract expired March 31, 1977.

Publication: Early Correlates of Speech, Language and Hearing. Lassman, F.M., Fisch, R.O., Vetter, D.K., and LaBenz, E.S. Edited by LaBenz, P.J. and LaBenz, E.S. Littleton, Massachusetts, PSG Publishing Company, Inc., in press.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1978 through September 30, 1979

UNIVERSITY OF MICHIGAN (NO1 NS 5-2308)

TITLE: Physical Growth Analysis

Contractor's Project Director: Stanley M. Garn, Ph.D.

Current Annual Level: \$ 00.00

Objectives: To develop the physical growth measurement data on the 50,000 children examined within the framework of the NINCDS Collaborative Perinatal Project (NCPP). Specifically:

1. Develop for body weight, length, chest circumference and head circumference, a set of tabular, percentile, normative tables of (a) size-for-age, (b) increments of size for age-interval, (c) size-for-size for age and size for gestation length for whites, blacks and Puerto Ricans separately and for boys and girls separately. This set of tables is largely intended as a reference document for the NINCDS Collaborative Perinatal Project.
2. Develop a set of summary tabulations and reports, directed to the major pediatric and growth-related users, complete with narrative and graphs, with the purpose of providing in the professional literature both an account of major substantive findings, and an in-the-literature account of the major data based along lines described in 1, but simplified as necessary.
3. To correlate the incidence and prevalence of dental and facial abnormalities with neurological defects, congenital abnormalities and other disorders of childhood.

Major Findings: Findings are reflected in publication to date.

Significance to the Program: The findings support previous study findings and are important to the pediatric community as well as to physical anthropologists in that they represent results from the largest longitudinal data base yet studied in the U.S.

Proposed Course: To complete the planned series of publications reflecting results and interpretation of analyses and to prepare a comprehensive, monograph-length report of findings generated during the course of the contract.

In addition to investigative research, preliminary chapter headings have been developed for the growth monograph required under this contract and are as follows:

Monograph Title: Determinants of Size and Growth in Infancy and Childhood

Chapter headings:

1. Introduction
2. Maternal size
3. Placental size and growth
4. Maternal maturational timing as a factor in child growth
5. Maternal smoking and effects on the offspring
6. Gestation length and subsequent growth
7. Birth size as a determinant of size and subsequent growth
8. The birth weight factor and subsequent growth
9. Head circumference and its implications
10. Bivariate growth (size for size)
11. Race, ethnic group and prenatal growth
12. Race and ethnic group in postnatal growth and development
13. Incremental growth
14. Familial aspects of growth and development
15. Growth and teeth

Course of Contract: Extended May 1, 1979 through October 31, 1979 without additional funds.

Publications:

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Black-White hemoglobin differences during pregnancy. Ecol. Food & Nutr. 5:99-100, 1976.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Birth size and growth appraisal. J. Pediatr. 90:1049-1051, 1977.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Effect of maternal smoking on hemoglobins and hematocrits of the newborn. (Letters to the Editor) Am. J. Clin. Nutr. 31:557-558, 1978.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Effect of socioeconomic status on early growth as measured by three different indicators. Ecol. Food & Nutr. 7:51-55, 1978.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Dose response effect of maternal smoking. (Letters to the Editor) Pediatrics 62:861-862, 1978.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Maternal smoking as a nutritional variable. Ecol. Food & Nutr. 7:143-145, 1978.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Effect of maternal smoking on weight and weight gain between pregnancies. Am. J. Clin. Nutr. 31:1302-1303, 1978.

Garn, S.M., and Bailey, S.M.: Genetics of maturational processes.' In Falkner, F., and Tanner, J.M., (Eds.): Human Growth. New York, Plenum Press, 1:307-330, 1978.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: The differential socioeconomic effect on the male. Am. J. Phys. Anthropol., in press.

Garn, S.M., Hoff, K., and McCabe, K.D.: Maternal fatness and placental size. Am. J. Clin. Nutr. 32:277-279, 1979.

Garn, S.M., Hoff, K., and McCabe, K.D.: Effect of placental size on the progeny of obese women. Ecol. Food & Nutr., in press.

Garn, S.M., Osborne, R.H., and McCabe, K.D.: Effect of prenatal factors on crown dimensions. Am. J. Phys. Anthropol., in press.

Garn, S.M., Hoff, K., and McCabe, K.D.: Is there nutritional mediation of the smoking effect on the fetus? Am. J. Clin. Nutr., in press.

Garn, S.M., Robinow, M., and Bailey, S.M.: Genetic and nutritional interaction in growth and development. In Jelliffe, D.B., and Jelliffe, E.F.P. (Eds.): Nutrition and Growth. New York, Plenum Press, Vol. 1, in press.

Garn, S.M.: Optimal nutritional assessment. In Jelliffe, D.B., and Jelliffe, E.F.P. (Eds.): Nutrition and Growth. New York, Plenum Press, Vol. 1, in press.

Garn, S.M.: Continuities and change in maturational timing. In Grim, O.G., and Kagan, J. (Eds.): Constancy and Change in Human Development. Cambridge, Harvard University Press, in press.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1978 through September 30, 1979

THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PA. (NO1 NS 7-2376)

TITLE: Analysis of General and Placental Pathology Data

Contractor's Project Director: Richard L. Naeye, M.D.

Current Annual Level: \$ 17,000 added to Contract for 6 months beginning January 31, 1979.

Objectives: The objectives of the current and proposed extension of the contract are (1) to complete the determination of the effects of smoking on the fetus, (2) a further explanation of the relationship between prepregnancy weight for height and placental growth as related to fetal growth and pregnancy outcome, and (3) a determination if selected factors this far examined have an independent influence on long term psychomotor development in NCPP children.

Major Findings: Findings are reflected in publications to date.

Course of Contract: January 31, 1979 through July 31, 1979. The Contractor has asked for an extension through December 31, 1979 with no additional funds.

Publications:

Naeye, R.L.: Sudden infant death syndrome: a prospective study. Am. J. Dis. Child. 130:1207-1210, 1976.

Naeye, R.L.: Placental infarction leading to fetal or neonatal death: a prospective study. Obstet. Gynecol. 50:583-588, 1977.

Naeye, R.L.: Placental abnormalities in victims of the sudden infant death syndrome. Biol. Neonate 32:189-192, 1977.

Naeye, R.L.: Causes of perinatal mortality in the U.S. Collaborative Perinatal Project. JAMA 238:228-229, 1977.

Naeye, R.L., Tafari, N., Judge, D., and Marboe, C.C.: Twins: causes of perinatal death in 12 United States cities and one African city. Am. J. Obstet. Gynecol. 131:267-272, 1978.

Naeye, R.L., and Peters, E.C.: Amniotic fluid infections with intact membranes leading to perinatal death: a prospective study. Pediatrics 61:171-177, 1978.

Naeye, R.L., and Dixon, J.B.: Distortions in fetal growth standards. Pediatr. Res. 12:987-991, 1978.

Naeye, R.L.: Causes of perinatal mortality excess in prolonged gestations. Am. J. Epidemiol. 108:429-433, 1978.

Naeye, R.L.: Effects of maternal cigarette smoking on the fetus and placenta. Br. J. Obstet. Gynaecol. 85:732-737, 1978.

Naeye, R.L.: Amniotic fluid infections, neonatal hyperbilirubinemia, and psychomotor impairment. Pediatrics 62:497-503, 1978.

Naeye, R.L.: Placenta previa: predisposing factors and effects on the fetus and surviving infants. Obstet. Gynecol. 52:521-525, 1978.

Naeye, R.L.: Underlying disorders responsible for the neonatal deaths associated with low apgar scores. Biol. Neonate 35:150-155, 1979.

Naeye, R.L.: Reliability factors of delivery due dates. J. Reprod. Med. 22:148-150, 1979.

Naeye, R.L.: Causes of the excessive rates of perinatal mortality and prematurity in pregnancies complicated by maternal urinary-tract infections. N. Engl. J. Med. 300:819-823, 1979.

Naeye, R.L. and Friedman, E.A.: Causes of perinatal death associated with gestational hypertension and proteinuria. Am. J. Obstet. Gynecol. 133: 8-10, 1979.

Naeye, R.L.: Neonatal apnea: underlying disorders. Pediatrics 63:8-12, 1979.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1978 through September 30, 1979

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS: (N01-NS-7-2377)

TITLE: A Prospective Cohort Epidemiologic Study of Learning Handicaps in Children Attending School

Contractor's Project Director: Alan Leviton, M.D.

Current Annual Level: \$111,888.00

Objectives: Conduct analyses of antecedents of school behavior and school achievement at age 9 in an identified sample of children in the Boston component of the NINCDS Collaborative Perinatal Project (NCPP) for the purpose of identifying risk factors for learning disorders.

Major Findings: Five learning handicaps in boys and six in girls have been identified as outcomes of interest. Antecedents are being analysed by epoch--e.g.--pre-pregnancy, pregnancy, delivery, early postnatal. Risk factors for learning handicaps include low family income, large family size, prior abortions, and some complications of pregnancy.

Course of Contract: September 30, 1977 through September 29, 1979. The contractor has asked for an extension, with additional funds, to complete work.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1978 through September 30, 1979

BETH ISRAEL HOSPITAL, BOSTON, MASSACHUSETTS (N01-NS-8-2381)

Title: Comprehensive Study of Labor and Delivery Effects on Offspring

Contractor's Project Director: Emanuel A. Friedman, M.D.

Current Annual Level: \$ 69,000

Objectives: The objectives are (1) to determine the effects on the fetus and the surviving infant of clinically definable labor factors, labor disorders and the spectrum of delivery procedures, and thus to identify and quantitate the specific risk factors in labor and delivery that contribute to perinatal mortality and to the development of long-term neurological and developmental disorders in children, and (2) to determine relationships between the various types of maternal anesthesia-analgesia and development of the child; specifically, to examine in detail the time-dose relationships and drugs used in combination during the course of labor and delivery, in relation to long-term neurological outcome in the child.

Major Findings: Work on the contract has progressed and the required report following Phase II has been received. Phase III objectives are now underway. During Phase II the contractor determined labor incremental durations, assessed progression patterns, defined distributions of dilatation and descent parameters, quantified outcome effects of these labor variables, identified dysfunctional labors, and investigated outcome effects of disordered labor patterns. In addition, error analysis which had been undertaken in Phase I was continued.

Course of Contract: March 13, 1978 through March 12, 1982. A fourth year was requested in the original proposal.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01163-17 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Selected Maternal Risk Factors and Congenital Cardiovascular Anomalies		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> PI: L. Bajda OTHER: A. Naylor </div> <div style="width: 30%;"> Medical Consultant Research Geneticist </div> <div style="width: 30%;"> DNB, NINCDS DNB, NINCDS </div> </div>		
COOPERATING UNITS (if any)		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: <div style="text-align: center;">1.5</div>	PROFESSIONAL: <div style="text-align: center;">1.0</div>	OTHER: <div style="text-align: center;">0.5</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS </div> <div> <input checked="" type="checkbox"/> (b) HUMAN TISSUES </div> <div> <input type="checkbox"/> (c) NEITHER </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div> <input checked="" type="checkbox"/> (a1) MINORS </div> <div> <input type="checkbox"/> (a2) INTERVIEWS </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p> This project uses data from the NINCDS Collaborative Perinatal Project to investigate the relation of selected <u>factors</u> which may affect the mothers <u>during pregnancy</u>, with the occurrence of <u>congenital heart defects</u> in the children. Observations on some 50,000 pregnancy records provide case and control data for analysis. Some 460 children have been identified as having definite congenital cardiac anomalies. These include cardiac conditions which are part of known syndromes. Analysis considers the problem as a whole, but also separates the various anomalies to clarify possible etiologies. </p>		

Project Description:

The Study has as its primary objective an epidemiologic investigation of relationships between maternal conditions and congenital cardiovascular anomalies. Identification of conditions putting the child "at risk" are sought.

Additional objectives include relating early signs of cardiac abnormality to cardiac diagnosis, growth, and mental status at 7-8 years of age as well as at intermediate levels. Emphasis on clinical attributes of the congenital heart case at various ages as well as the maternal history involved may provide a ready guide to the optimal care of the child.

Methodology

Study records from the NINCDS Collaborative Perinatal Project (approximately 50,000 population) provide the data. Case number print-outs for children diagnosed as suspect or definite cardiacs on the one-year and seven-year summaries are used as indicators for the records searched for preselected maternal variables. After tabulation, analysis and comparison with computer provided control data, the use of statistical techniques should present a maternal "profile" for the infant "at risk" for congenital cardiovascular disease.

Current status and major findings

Preliminary findings on an initial sample of 112 definite congenital cardiac cases emphasized the need for a larger study group in order that the maternal factors could be related to a specific diagnosis. From a pool of over 660 suspected cases, 390 were identified as having non-syndromic congenital heart disease. Special protocols for abstraction of selected obstetric, pediatric and family history variables have been designed, and abstraction of this information for cases has been completed. Cardiac diagnoses have been tabulated and coded. Selection of controls and design of analysis are in progress.

Proposed course

Selection of controls, abstraction of relevant information for controls as for cases, and analysis.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01184-17 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Population Dynamics of Tay-Sachs Disease and Other Sphingolipidoses		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div>PI: N.C. Myrianthopoulos</div> <div>Research Geneticist</div> <div>DNB NINCDS</div> </div>		
COOPERATING UNITS (if any) Dr. D. Gröschel, University of Texas		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .00	PROFESSIONAL: .00	OTHER: .00
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <div style="margin-top: 20px;"> <p>The objective is to confirm experimentally the epidemiologic finding that the <u>selective advantage</u> of the <u>TSD heterozygote</u> is due to possible <u>protection of the heterozygote from tuberculosis</u>. Current experiments measure the <u>phagocytic activity of mouse macrophages</u> for mycobacteria in the presence and absence of <u>GM₂ ganglioside</u>.</p> </div>		

Project Description:

Objectives: To confirm experimentally the epidemiologic finding that the selective advantage of the Jewish TSD heterozygote is due to possible protection of the heterozygote from tuberculosis.

Methodology: The experimental design is to measure the rate of growth of the mycobacterium tuberculosis in media with and without hexosaminidase A, and the rate of infection by the mycobacterium of tissues with and without lipid accumulation. Experiments have been designed in which mouse macrophages are fed GM₂ ganglioside in vivo and in vitro, and the phagocytic activity for mycobacteria measured. Due to technical difficulties, this project has been suspended.

Major findings: None

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01274-15 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Genetic Bases of Neonatal Reflexes		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div style="width: 30%;"> PI: A.F. Naylor OTHER: N.C. Myrianthopoulos </div> <div style="width: 30%;"> Research Geneticist Research Geneticist </div> <div style="width: 30%; text-align: right;"> DNB NINCDS DNB NINCDS </div> </div>		
COOPERATING UNITS (if any) None		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER: .00
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p style="margin-top: 20px;"> <u>Neonatal reflexes</u> (suck, rooting, palmar grasp, plantar grasp, Moro, etc.) are usually tested as signs of neurological and general well-being. A study has long been planned as to whether genetic variables may be sometimes responsible for absence of specific reflexes. A data file which contains genetic and background information has been enlarged to include data on <u>neonatal reflexes</u> so that the investigation can finally be carried out. </p>		

Project Description:

Objectives: To investigate the validity of regarding the suck, rooting and other neonatal reflexes as genetic entities.

Major findings: A review of cases has led to criteria for accepting children as normal but lacking specific reflexes and rejecting those cases which are clearly abnormal. Appropriate codes, in the same format as malformations, have been included in the now completed Family Analysis File, which includes items on most possible abnormalities (physical or mental), background variables and relationships to other NCPP children.

Proposed Course: These variables will be analyzed familiarly by methods under development for all variables in the Family Analysis File. Special supplementary analyses will be carried out.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01276-15 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Sequential Aspects of Occurrence of Spontaneous Abortion in Family Histories		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div>PI: A.F. Naylor</div> <div>Research Geneticist</div> <div>DNB NINCDS</div> </div>		
COOPERATING UNITS (if any) D. Warburton, College of Physicians and Surgeons at Columbia University		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: <div style="text-align: right;">.20</div>	PROFESSIONAL: <div style="text-align: right;">.20</div>	OTHER: <div style="text-align: right;">.00</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <div style="margin-top: 20px;"> <p>The objective of this study has been to relate the risk of <u>spontaneous abortion to maternal age</u> and prior reproductive experience. Careful reconsideration of long available tabulations has shown convincingly that gravidity is a major correlate of spontaneous abortion and maternal age is of no importance. A paper making these points has been published by <u>Fertility and Sterility</u>.</p> </div>		

Project Description:

Objectives: To relate the risk of spontaneous abortion to maternal age and prior reproductive experience. A special point under investigation is whether apparent age effects are explicable by a tendency for intrinsic habitual aborters to remain in the reproductive population longer in attempts to compensate for unsuccessful pregnancies. Also conditional risks have been estimated.

Proposed course: A paper arguing that age effects are real but laying emphasis on the decided importance of parity effects has already been published. Reconsideration of data tabulated from OB-2 forms has shown the following: (1) the anamnestic reproductive histories are statistically reliable; (2) maternal age does not affect abortion risk once prior reproductive experience is taken into account; (3) gravidity effects are responsible for upwards of 30% of spontaneous abortions.

A paper making these points and setting out a conditional table has been published by Fertility and Sterility.

Publications:

Naylor, A.F. and Warburton, D.: Sequential aspects of spontaneous abortion. II. Collaborative Study data show that gravidity determines a very substantial rise in risk. Fertil. Steril. 31:282-286, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01514-13 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Record Linkage of Relatives Registered in the Collaborative Study		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div> PI: A.F. Naylor OTHER: N.C. Myrianthopoulos </div> <div> Research Geneticist Research Geneticist </div> <div> DNB NINCDS DNB NINCDS </div> </div>		
COOPERATING UNITS (if any) None		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: <div style="text-align: right;">.55</div>	PROFESSIONAL: <div style="text-align: right;">.55</div>	OTHER: <div style="text-align: right;">.00</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <div style="margin-top: 20px;"> <p>A file has been created which can link NINCDS Collaborative Perinatal Project data for women with relatives also in the Project. This has been imbedded in a <u>file</u> which classifies registrants by the number of Project pregnancies if they have no relatives registered. This larger file, has in turn, been merged with a file containing other <u>genetic</u> information, such as <u>twin zygosity</u>, and <u>medical and psychological</u> data for familial studies of malformations and other conditions. The record linkage file, as such, will not be changed unless experience in its use shows it to be erroneous or cumbersome.</p> </div>		

Project Description:

The objective of this study is to identify all relatives of graviorae registered in the NINCDS Collaborative Perinatal Project and link their records to facilitate genetic studies of obstetric, pediatric, psychological and sensory data.

The main record linkage file and its auxiliaries have been completed. Although it is being preserved as a separate file, on one set of magnetic tapes, it has also been merged with medical and psychological data preliminary to actual use in genetic and family studies.

Tabulations have been produced indicating that enough familial information is present to make analyses of not very rare abnormalities quite feasible.

This project has been completed.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01515-13 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Rh Hemolytic Disease in Negro and White Infants		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 30%;">PI: A.F. Naylor</div> <div style="width: 35%;">Research Geneticist</div> <div style="width: 30%;">DNB NINCDS</div> </div>		
COOPERATING UNITS (if any) None		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: <div style="text-align: right;">.00</div>	PROFESSIONAL: <div style="text-align: right;">.00</div>	OTHER: <div style="text-align: right;">.00</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 30%;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div> <div style="width: 30%;"> <input checked="" type="checkbox"/> (b) HUMAN TISSUES </div> <div style="width: 30%;"> <input type="checkbox"/> (c) NEITHER </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <div style="margin-top: 20px;"> <p>To carry out an investigation of a report in the literature that high <u>Rh</u> (but not <u>ABO</u>) antibody levels have smaller morbid effects in <u>black</u> than <u>white</u> babies, a data file under development, which is rich in information on both control and outcome variables, will be augmented with the needed laboratory test information.</p> </div>		

Project Description:

Objectives: To confirm a report that high Rh antibody levels have smaller morbid effects in Negro than in white babies, although this is not true for ABO antibodies.

Major findings: Preliminary and indirect confirmation has been obtained, from a small data sample under study, for reports in the literature that high Rh antibody titers are not as highly associated with serious morbidity in Negroes as in whites.

Proposed course: This project has been discontinued.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01754-11 DNB								
PERIOD COVERED October 1, 1978 to September 30, 1979										
TITLE OF PROJECT (80 characters or less) Growth and Intellectual Development of Children from Interracial Matings										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 15%;">PI:</td> <td style="width: 35%;">A.F. Naylor</td> <td style="width: 35%;">Research Geneticist</td> <td style="width: 15%;">DNB NINCDS</td> </tr> <tr> <td>OTHER:</td> <td>N.C. Myrianthopoulos</td> <td>Research Geneticist</td> <td>DNB NINCDS</td> </tr> </table>			PI:	A.F. Naylor	Research Geneticist	DNB NINCDS	OTHER:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS
PI:	A.F. Naylor	Research Geneticist	DNB NINCDS							
OTHER:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS							
COOPERATING UNITS (if any) L. Willerman, Department of Psychology, University of Texas at Austin										
LAB/BRANCH Developmental Neurology Branch										
SECTION Birth Defects and Genetic Disorders Section										
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205										
TOTAL MANYEARS: <div style="text-align: right;">.10</div>	PROFESSIONAL: <div style="text-align: right;">.10</div>	OTHER: <div style="text-align: right;">.00</div>								
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS										
SUMMARY OF WORK (200 words or less - underline keywords) A small subpopulation within NINCDS Collaborative Perinatal Project children has been identified as being of mixed <u>black</u> and <u>white</u> parentage. Within the <u>interracial</u> group of matings there is no evidence that genetic or socio-economic differences are related to race of mother (or father). Thus socio-psychological influences, presumably operating through mother-child interactions, can be examined indirectly. Two papers have been published which indicate that, although early childhood differences are wholly negligible, children of white mothers eventually develop positive intellectual differences. A paper analyzing longitudinal differences in early growth rates will be published.										

Project Description:

Results of analyses of growth and intellectual development have been prepared for separate publication.

The conclusion reached in an initial publication in Science, that analyses of NCPP interracial matings for IQ data indicate that race of mother as a post-natal environmental indicator accounts for much of the black-white IQ differences, has been strengthened in a paper published last year. Analyses of Bayley Mental and Motor Scores, taken at 8 months, when maternal social influences will have had little effect show no differences between children of black/white and white/black matings. Also a more convincing demonstration has been made of lack of bias in genetic or socio-economic factors affecting four year IQ on the paternal side.

The physical development data have been re-analyzed to compare all properly selected NCPP interracial and monoracial matings. Hospital variation and other background factors were corrected for by multivariate regression. At birth children born to white mothers, whether by white or black fathers, are very similar in weight and length. Monoracial blacks are definitely smaller and interracials with black mothers may be intermediate in size (small numbers cloud the issue). At four months interracials with white mothers fall behind in weight (but catch up after one year), perhaps because of social stresses in the household. A manuscript laying out these points has been accepted by Social Biology.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 01857 - 10 DNB						
PERIOD COVERED October 1, 1978 to September 30, 1979								
TITLE OF PROJECT (80 characters or less) The Genetics of Intellectual and Motor Performance								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: Sarah H. Broman</td> <td style="width: 33%;">Acting Chief, MRLDS</td> <td style="width: 33%;">DNB NINCDS</td> </tr> <tr> <td>Other: Paul L. Nichols</td> <td>Research Psychologist</td> <td>DNB NINCDS</td> </tr> </table>			PI: Sarah H. Broman	Acting Chief, MRLDS	DNB NINCDS	Other: Paul L. Nichols	Research Psychologist	DNB NINCDS
PI: Sarah H. Broman	Acting Chief, MRLDS	DNB NINCDS						
Other: Paul L. Nichols	Research Psychologist	DNB NINCDS						
COOPERATING UNITS (if any) None								
LAB/BRANCH Developmental Neurology Branch								
SECTION Mental Retardation and Learning Disorders Section								
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205								
TOTAL MANYEARS: .15	PROFESSIONAL: .10	OTHER: .05						
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) Familial influences on tests of mental and motor performance at ages four and seven were examined by comparing correlation coefficients among monozygotic <u>twins</u> , dizygotic twins, full <u>siblings</u> , half siblings, and cousins within race, sex, and social class groups. The correlations between scores of twin and sibling pairs on the Stanford-Binet (age 4) and Wechsler (age 7) <u>intelligence tests</u> suggested a greater <u>genetic influence</u> than was found for infant test scores.								

Project Description:

This study assessed the contribution of genetics to the variance in intellectual and motor performance at eight months, four years, and seven years by comparing scores among twins, siblings, half siblings and cousins. Four year developmental indices included the Stanford-Binet IQ, Graham Block Test, fine and gross motor scores, height, weight, and head circumference. Seven year correlations were calculated for WISC verbal, performance, and total IQ, WISC subtests, Bender-Gestalt scores, Draw-A-Person Test, Auditory-Vocal Association Test (ITPA), Wide Range Achievement Tests, height, weight, and head circumference. A report has been published on genetics of infant mental test performance, in which scores of twins and singletons were compared. The estimated relative genetic influence on the variability of the four and seven year measurements ranged from high (physical measurements at seven years) to moderate (IQ at four and seven years) to low (some WISC subtests). The genetic influence on four and seven year indices appeared greater than that found for psychomotor performance in infancy.

Proposed Course: A final paper is in preparation.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02052-07 DNB
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) The First Year of Life		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div> PI.: J. S. Drage Other: E. C. Jackson </div> <div> Chief formerly, Biostatistician </div> <div> DNB, NINCDS OBE, NINCDS </div> </div>		
COOPERATING UNITS (if any) J. B. Hardy, The Johns Hopkins University		
LAB/BRANCH Developmental Neurology Branch		
SECTION Office of the Chief		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Md. 20205		
TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS </div> <div> <input checked="" type="checkbox"/> (b) HUMAN TISSUES </div> <div> <input type="checkbox"/> (c) NEITHER </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div> <input checked="" type="checkbox"/> (a1) MINORS </div> <div> <input type="checkbox"/> (a2) INTERVIEWS </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p> "The First Year of Life" is a volume reporting on the frequency distribu- tion of a number of findings reported on NINCDS Collaborative Perinatal Project children during the first year of their lives. It includes information on <u>birthweight-gestation distribution</u>, <u>bilirubin levels</u>, age at hospital discharge, and distributions of various pathological findings detected during the nursery stay and during the first year of life. Of particular interest is the infor- mation regarding <u>brain abnormality</u> as detected during the nursery period. This volume is intended to serve as a general <u>description</u> of the Collaborative Project children during their first year of life and as a reference document for further in-depth studies. The document is in press and publication is expected summer, 1979. </p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02058-07 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Convulsive Disorders Data Analysis Group		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div> PI: K.B. Nelson PI: J.H. Ellenberg </div> <div> Pediatric Neurologist Mathematical Statistician </div> <div> DNB NINCDS OBE NINCDS </div> </div>		
COOPERATING UNITS (if any) Dr. J. Freeman, Johns Hopkins Dr. K. Holden, Johns Hopkins OBE, NINCDS		
LAB/BRANCH Developmental Neurology Branch		
SECTION Section on Cerebral Palsy and Other Motor Disorders		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.6	OTHER: 0.3
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div> <div> <input checked="" type="checkbox"/> (b) HUMAN TISSUES </div> <div> <input type="checkbox"/> (c) NEITHER </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) This study examines the relationship between perinatal factors and the occurrence of <u>seizure disorders</u> in childhood in a large, prospectively studied population. In addition to the central question of etiology, it investigates frequency, prognosis, demographic characteristics, and a number of other aspects of these disorders. Extensive hand review and classification of cases has been completed, and files created. Univariate screen of maternal, obstetric, and pediatric risk factors, and demographic analysis, have been completed. File creation for multivariate analysis is partially complete, and regression analyses have begun. Selected topics of particular clinical relevance are under examination.		

Project Description:

Project No. Z01 NS 02058-07 DNB

Objectives: To examine maternal characteristics, conditions of pregnancy, labor, delivery and the neonatal period, and illness and injuries of early childhood for their association with seizure disorders. To seek clinically useful indices for prediction, to evaluate clustering of other handicaps with convulsive disorders, and to examine the frequency of seizure disorders in the population of the NINCDS Collaborative Perinatal Project.

Methodology: The preliminary program to screen antecedent obstetric variables and early clinical manifestations with regard to their association with seizure disorder diagnoses has been completed. The analysis of demographic factors (e.g., institution, race, socioeconomic status, etc.) and their impact on the incidence and risk of seizure disorders is now available, and is in the process of assessment. A study into the natural history of seizure disorders from one to seven years of life is underway, taking full advantage of the prospective nature of the NINCDS Collaborative Perinatal Project.

Drs. Freeman and Holden are participating in the study of the prognosis of neonatal seizures, and have presented some of their findings at an international meeting.

Major Findings: Approximately one in twenty children (57/1000) followed to the age of seven years had at least one seizure. About one-tenth that number (4.8/1000) had active epilepsy by the age of seven. As studied in the NINCDS Collaborative Perinatal Project, active epilepsy in childhood is slightly more common in girls than boys, and approximately equal in rate in whites and blacks.

A major substudy on febrile seizures (Z01 NS 02234-04 DNB) is described separately. Three reports have been published and another has been submitted for publication. It is proposed to follow up these studies with a survey to establish current practice with regard to the management of febrile seizures by the various medical subspecialties - and to hold a consensus meeting with regard to the questions of management.

Data on the prevalence of specific seizure disorders in early childhood are now available, and a manuscript is in preparation on this subject.

Approximately a quarter of children with epilepsy in early childhood have another major neurological handicap: mental retardation or cerebral palsy, or both. The other three-quarters of epileptic children did not have these additional disabilities. Analysis of the antecedents and clinical course in these two major groups is in progress.

Seizures occurring in the first month of life were associated with a relatively high rate of death or subsequent disability, including cerebral palsy. Neonatal seizures are a major marker of risk for subsequent neurologic morbidity.

A report is in press concerning birthweight and gestational age as risk factors for seizure disorders. Low birthweight, immaturity and smallness for dates at term were not important antecedents of epilepsy in children free of cerebral palsy. Maternal, obstetrical, and early childhood characteristics which are associated with seizure disorders are now under study.

Future Course: Demographic data on convulsive disorders in Study children, and the univariate screen of antecedent maternal and pediatric characteristics are now complete. Multivariate analysis has begun. Selected topics of particular medical importance will be examined in sub-studies. A monograph on convulsive disorders in childhood will be prepared; target date is July, 1981.

Significance: The convulsive disorders are a common and socially costly medical problem. It is estimated that about 4 million Americans have some form of epilepsy. The cost of the epilepsies in direct payments and medical expenses has been calculated at more than \$4 billion per year. The information generated in the NINCDS Collaborative Perinatal Project may contribute useful information in this important problem area.

Publications: Ellenberg, J.H. and Nelson, K.B.: Birthweight and gestational age in children with cerebral palsy or seizure disorders. Am. J. Dis. Ch., in press.

See Febrile Seizures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02059-07 DNB						
PERIOD COVERED October 1, 1978 to September 30, 1979								
TITLE OF PROJECT (80 characters or less) Cerebral Palsy Data Analysis Group								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%;"> <tr> <td style="width: 33%;">PI: K.B. Nelson</td> <td style="width: 33%;">Pediatric Neurologist</td> <td style="width: 33%;">DNB NINCDS</td> </tr> <tr> <td>PI: J.H. Ellenberg</td> <td>Mathematical Statistician</td> <td>OBE NINCDS</td> </tr> </table>			PI: K.B. Nelson	Pediatric Neurologist	DNB NINCDS	PI: J.H. Ellenberg	Mathematical Statistician	OBE NINCDS
PI: K.B. Nelson	Pediatric Neurologist	DNB NINCDS						
PI: J.H. Ellenberg	Mathematical Statistician	OBE NINCDS						
COOPERATING UNITS (if any) None								
LAB/BRANCH Developmental Neurology Branch								
SECTION Section on Cerebral Palsy and Other Motor Disorders								
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205								
TOTAL MANYEARS: 1.2	PROFESSIONAL: 0.8	OTHER: 0.4						
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) <p>This large prospective study attempts to add to available knowledge of the <u>perinatal factors</u> associated with <u>motor handicaps</u> in childhood, the primary goal being to identify areas for possible preventive efforts.</p> <p>A study on the <u>prevalence</u> of cerebral palsy has been published. Data on demographic analysis and a univariate screen of <u>maternal and pediatric factors</u> associated with <u>cerebral palsy</u> are available. Multivariate analysis is underway.</p>								

Project Description:

Project No. Z01 NS 02059-07 DNB

Objectives: To examine the etiology of motor disabilities in children, to improve clinical prediction, and to examine the relative frequencies of motor and associated disabilities in the population of the NINCDS Collaborative Perinatal Project.

Methodology: The univariate screen relating antecedent obstetric variables and early clinical manifestations with regard to their association with cerebral palsy diagnoses has been completed and multivariate analyses have begun. The analysis of demographic factors (e.g., institution, race, socioeconomic status, etc.) and their impact on the incidence and risk of cerebral palsy is available. Study of the natural history of cerebral palsy from one to seven years of life has been performed, taking full advantage of the prospective nature of the NINCDS Collaborative Perinatal Project.

Future Course: The multivariate analysis of the obstetric, early clinical and demographic factors is under way. Extensive use is being made of the NEUROMED statistical package developed in the Office of Biometry and Epidemiology to facilitate the execution of this complicated last phase of analysis.

Major Findings: Cerebral palsy at seven years is somewhat more frequent in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma.

Clearly handicapping cerebral palsy was present at age seven in 22-33/10,000 children, the range being related to race and sex. Within each birthweight and gestational age group examined, white males were at highest risk of cerebral palsy.

A listing of maternal and pediatric conditions most strongly associated with cerebral palsy outcomes has been made, and is the basis for multivariate analysis.

Studies have been completed concerning:

1. The relationship of birthweight and gestational age to cerebral palsy (CP). Although low birthweight and immaturity are risk factors for CP, 59% of CP and 69% of CP other than spastic diplegia, occurred in infants of term weight and full 37 or more weeks gestational age. Preterm infants with later CP tended to be undergrown even considering their short gestations.
2. Signs of neonatal neurologic dysfunction as predictors of CP. Certain signs on neonatal neurological examinations, and observations in the newborn nursery, are strongly associated with the likelihood of later CP. This study permits evaluation of the potential utility of neonatal mass screening programs for motor deficits.

Studies are now in progress concerning:

1. Apgar scores as predictors of longterm neurologic morbidity. Very low Apgar scores at ten, 15 and 20 minutes identify surviving babies at high risk for CP, which in this circumstance is normally accompanied by severe mental retardation and often by seizure disorders.
2. Early recognition of the infant at high risk for CP. Findings on examination at four months of age are being evaluated for utility in the early recognition of infants at risk for motor handicap. An infant who was considered to be neurologically abnormal at age four months, was at 100 times the risk of CP at age seven years as a baby who was considered neurologically normal when four months old.
3. Associated handicap in children with CP. In addition to motor disability, children with CP have an increased frequency of intellectual, sensory and behavioral disorders, and seizure disorders. This study quantifies the degree of the association of CP with other handicaps, according to severity of CP and to specific CP type.
4. Children who "outgrew" CP. Subjects who were free of CP at seven years were more likely to be mentally retarded, to have recurrent convulsions, speech articulation problems, and other disabilities if they had shown abnormal motor signs on examination at one year of age. Children with documented early motor abnormalities, especially those of mild degree, may be free of motor handicaps by early school age but at risk for other disabilities.

Significance: Approximately 750,000 persons in the United States are victims of cerebral palsy; milder forms of cerebral palsy are more frequent still. The loss in social and economic terms is immense, and individuals with CP are often lifelong dependents of their families or the state. Our aims are to identify areas in which preventive efforts may be effectively directed, to improve clinical prognostication, to examine clustering of handicaps, and to estimate relative frequency of cerebral palsy conditions.

Publications: Ellenberg, J.H. and Nelson, K.B.: Birthweight and gestational age in children with cerebral palsy or seizure disorders. Am. J. Dis. Child., in press.

Nelson, K.B. and Ellenberg, J.H.: Neonatal signs as predictive of cerebral palsy. Pediatrics 64:225-232, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02060-07 DNB
PERIOD COVERED October 1, 1978 through September 30, 1979		
TITLE OF PROJECT (80 characters or less) Birthweight-Gestational Age		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> PI: B. H. Williams Other: J. S. Drage </div> <div style="width: 30%;"> Assistant Head Chief </div> <div style="width: 30%;"> CPS, DNB, NINCDS DNB, NINCDS </div> </div>		
COOPERATING UNITS (if any) J. B. Hardy, The Johns Hopkins University E. D. Mellits, The Johns Hopkins University		
LAB/BRANCH Developmental Neurology Branch		
SECTION Collaborative Perinatal Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.50	PROFESSIONAL: 0.25	OTHER: 0.25
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) During the past year <u>Phase II</u> , a <u>multivariant analysis</u> to determine the relationship of <u>birthweight</u> as the <u>dependent variable</u> to a large number of <u>antecedent</u> (prenatal) <u>independent variables</u> , has been completed. The examination of a <u>Birthweight Index</u> derived from Phases I and II to determine its <u>predictive value</u> for birthweight-gestational age <u>outcomes</u> has been completed. A monograph is being prepared under personal services contracts with J. B. Hardy and E. D. Mellits.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02062 - 07 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Minimal Brain Dysfunction		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div> PI: P. L. Nichols Other: Ta-chaun Chen </div> <div> Research Psychologist Sr. Math. Statistician </div> <div> DNB NINCDS OBE NINCDS </div> </div>		
COOPERATING UNITS (if any) None		
LAB/BRANCH Developmental Neurology Branch		
SECTION Mental Retardation and Learning Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .90	PROFESSIONAL: .70	OTHER: .20
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) Antecedents of minimal brain dysfunction were investigated by examining the association of three major symptoms--school achievement, or <u>learning difficulties</u> ; <u>hyperkinetic-impulsive behavior</u> ; and minor neurological problems, or <u>neurological soft signs</u> -- with socioeconomic, perinatal, developmental, and familial variables. A major report describing the project is nearly complete. Variables significantly associated with low achievement included socioeconomic status, number of family moves, family size, affected siblings, and behavior and motor performance at age 4. Hyperactivity was associated with cigarette smoking during pregnancy, size at birth and in infancy and childhood, father absent from the home, affected siblings, and behavior and motor performance at age 4. Associations with neurological signs included motor performance in infancy and at 4 years of age, cigarette smoking during pregnancy, size at birth and later, affected siblings, and neonatal seizures.		

Project Description:

Specific diagnoses of minimal brain dysfunction (MBD) have not been made for children in the longitudinal NINCDS Collaborative Perinatal Project, but there is information available related to the most frequently cited symptoms (e.g., hyperkinetic-impulsive behavior, learning difficulties, and neurological "soft signs"). This study has developed MBD criteria from the available NCPP data and characterized children with these symptoms in terms of demographic, psychological, and physical variables. Univariate analyses of the associations between MBD symptoms and hundreds of antecedent conditions have been performed. Many significant associations were found; some conditions related to poor school achievement were low socioeconomic status (including low levels of parental education, occupational status, and income; public assistance, and high housing density), frequent family moves, large family size, affected siblings, small size at birth and during infancy and later childhood, and abnormal behavior and motor performance at age 4. Hyperactivity was associated with cigarette smoking during pregnancy, absence of fathers from the home, small size at birth and later ages, being an "only child," affected siblings, abnormal motor performance and behavior at 8 months, and abnormal behavior and motor performance at 4 years. Neurological soft signs were related to poor motor performance at 8 months, neonatal seizures, cigarette smoking during pregnancy, small size at birth and later, affected siblings, and abnormal behavior and motor performance at age 4. Multivariate analyses have shown that most of the associations found remained significant when examined in combination with other variables. Familial associations were especially important. Of all the early predictors simultaneously examined, including socioeconomic status and perinatal complications, mean achievement score of siblings was the best discriminator between children with and without poor academic performance. The presence of a hyperactive sibling was the best discriminator between children with and without hyperactivity. And, presence of a sibling with neurological soft signs was one of the best discriminators between children with and without these conditions. A book length report describing the entire project is nearly complete.

Publications:

Rieder, R.O. and Nichols, P.L.: Offspring of schizophrenics III. Hyperactivity and neurological soft signs. Arch. Gen. Psychiatry. 36: 665-674, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02106 - 06 DNB									
PERIOD COVERED October 1, 1978 to September 30, 1979											
TITLE OF PROJECT (80 characters or less) Developmental Factors Associated with Mental Retardation											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: S. H. Broman</td> <td style="width: 33%;">Acting Chief, MRLDS</td> <td style="width: 33%;">DNB NINCDS</td> </tr> <tr> <td>Other: P. L. Nichols</td> <td>Research Psychologist</td> <td>DNB NINCDS</td> </tr> <tr> <td>J. P. Pomeroy</td> <td>Systems Analyst</td> <td>DNB NINCDS</td> </tr> </table>			PI: S. H. Broman	Acting Chief, MRLDS	DNB NINCDS	Other: P. L. Nichols	Research Psychologist	DNB NINCDS	J. P. Pomeroy	Systems Analyst	DNB NINCDS
PI: S. H. Broman	Acting Chief, MRLDS	DNB NINCDS									
Other: P. L. Nichols	Research Psychologist	DNB NINCDS									
J. P. Pomeroy	Systems Analyst	DNB NINCDS									
COOPERATING UNITS (if any) Dr. Peter Shaughnessy, University of Colorado Medical Center Dr. Wallace Kennedy, Florida State University											
LAB/BRANCH Developmental Neurology Branch											
SECTION Mental Retardation and Learning Disorders Section											
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205											
TOTAL MANYEARS: .7	PROFESSIONAL: .6	OTHER: .1									
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS											
SUMMARY OF WORK (200 words or less - underline keywords) Data collected in the NCPP have been analysed to define the primary and secondary contributions of specific <u>biological and environmental variables</u> to mental retardation in a population of 37,000 children followed from the prenatal period to age 7. The frequency of <u>severe retardation</u> was not found to differ by ethnic group, but <u>mild retardation</u> was more frequent among blacks than among whites. The incidence of mental retardation was negatively related to <u>social class</u> . Major neurological abnormalities were more frequent among the severely retarded than mildly retarded children, and more frequent among whites than blacks in both of the retarded groups. Within ethnic group, the proportion of neurologically involved retarded children was found to increase with social class. Identified risk factors for mental retardation include <u>urinary tract infections during pregnancy, teen-age pregnancy, clinical signs of perinatal anoxia, and poor psychomotor performance in infancy.</u>											

Project Description:

Objectives: Data collected in the NCPP were analysed to determine the primary and contributing roles of specific biological and environmental variables in mental retardation in a population of 37,000 children followed from the prenatal period to age 7. The identification of early signs of mental retardation will facilitate prevention, diagnosis and treatment, and will add substantially to the knowledge in this area that has been derived largely from small retrospective studies of institutionalized retardates.

Method: Mental retardation was defined as an IQ of 70 or less on the Weschler Intelligence Scale for Children, or, for the few children who could not be tested according to study protocol, equivalent IQs from other tests or reliable clinical judgements of retardation. Children with IQs under 70 were subdivided into four major categories consisting of those with severe retardation (IQ under 50) with and without signs of central nervous system damage, and those with mild retardation (IQ between 50 and 69) with and without such signs. Neurological diagnoses were obtained from the pediatric-neurological examination given at age seven. Comparison groups were composed of children with IQs in the borderline, average and superior ranges. Analyses were performed within ethnic group.

Major Findings:

The incidence of severe retardation (0.5%) did not differ by ethnic group, but mild retardation was more frequent among blacks (5%) than whites (1%). The incidence of mild retardation, and to a lesser extent severe retardation, decreased as social class increased. Among severely retarded children, three-fourths of the whites but only one-half of the blacks had major neurological problems. Among mildly retarded children, 14% of the whites and 6% of the blacks had major neurological problems. In general, the proportion of retarded children with major neurological involvement increased as social class increased.

Urinary tract infection during pregnancy has a strong independent association with severe mental retardation without major neurological involvement.

Adolescent childbearing is associated with low IQ scores (under 70) at age four, and among whites, at age 7.

Clinical signs of perinatal anoxia are associated with below-average cognitive development. The risk for mental retardation is greatest when signs of central nervous system impairment are also present.

Infant psychomotor test scores at 8 months are good predictors of severe mental retardation at age 7.

IQ scores at age 4 are good predictors of all levels of mental development at age 7.

Proposed Course: A monograph is in preparation.

Publications: Broman, S. H.: Perinatal Anoxia and Cognitive Development in Early Childhood. In Field, T., Sostek, A. M., Goldberg, S. and Shuman, H. H. (Eds): Infants Born at Risk. New York: Spectrum, 1979.

Broman, S. H. Long-term Development of Children Born to Teenagers. In Scott, K., Field, T., and Robertson, E. (Eds.): Teenage Parents and Their Offspring. New York: Grune and Stratton, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02107-06 DNB
PERIOD COVERED <p style="text-align: center;">October 1, 1978 through September 30, 1979</p>		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">The Study of Visual Abnormalities in the NINCDS Collaborative Perinatal Project</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 100px;"> <div>PI: R. Feinberg</div> <div>Research Psychologist</div> <div>DNB, NINCDS</div> </div>		
COOPERATING UNITS (if any) W.R. Baldwin, New England College of Optometry; R.E. Hoover, Baltimore, Md.; R.P. Kling, Georgetown Univ. Hosp.; M.A. Whitcomb, Nat. Acad. of Sc.; S.Z. Wood, Washington, D.C.; F.A. Young, Wash. State Univ.		
LAB/BRANCH <p style="text-align: center;">Developmental Neurology Branch</p>		
SECTION <p style="text-align: center;">Collaborative Perinatal Section</p>		
INSTITUTE AND LOCATION <p style="text-align: center;">NINCDS, NIH, Bethesda, Maryland 20205</p>		
TOTAL MANYEARS: <p style="text-align: center;">1.0</p>	PROFESSIONAL: <p style="text-align: center;">1.0</p>	OTHER: <p style="text-align: center;">0.0</p>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div><input checked="" type="checkbox"/> (a) HUMAN SUBJECTS</div> <div><input checked="" type="checkbox"/> (b) HUMAN TISSUES</div> <div><input type="checkbox"/> (c) NEITHER</div> </div> <div style="margin-top: 10px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p style="text-align: center;">This project includes the analysis between visual abnormalities in NCPP children and predictor variables; anecdotal treatment based on case histories of unusual visual abnormalities; special studies of <u>high-incidence disorders</u>; and an overview of <u>handedness</u> and <u>eye dominance</u> as ascertained in NCPP data; case studies of the <u>blind children</u>; and, preparation of a bibliography (monograph) encompassing these subjects.</p>		

Project Description:

The objectives of this project are to determine the extent to which genetic, maternal, obstetric, pediatric and environmental factors produce eye and visual abnormalities in the NCPP children; to assess the relative frequency of such anomalies; and, to study the concomitance of visual abnormalities with other sensory and motor neurological and systemic disorders.

Data analyses are now complete and the monograph report is in preparation. The following is an outline of the book as currently perceived.

1. Preface
2. Foreword
3. Introduction
4. The Collaborative Perinatal Study
 - Background of Study
 - Original Purpose
 - Expansion of Project
 - The Study Population, Cohort and Sample
 - Composition of the Study Population
 - Selection of the Collaborating Centers and of the Gravidas
 - Composition of the Study Population
 - Characteristics of Women Lost to the Study
 - Characteristics of the Mother and Family in the Study
 - Socioeconomic Considerations
- 5-A. Frequencies of Eye Conditions
- B. Vision Abnormalities in Relationship to the Total Study
- 6-7. Associations with Pediatric-Neurological Variables
8. Vision Screening
9. Correlations of One Year and Seven Year Variables
10. Referred Cases- - Anecdotal Reports
11. Special Studies: Prematurity; Retinal Hemorrhage
- 12-A. Appendices
- 12-A1. Glossary
- 12-A2. Forms Used
- 12-B. Index

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02108 - 06 DNB									
PERIOD COVERED October 1, 1978 to September 30, 1979											
TITLE OF PROJECT (80 characters or less) Developmental Factors Associated with Learning Disorders											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT											
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: S. H. Broman</td> <td style="width: 33%;">Acting Chief, MRLDS</td> <td style="width: 33%;">DNB NINCDS</td> </tr> <tr> <td>Other: E. C. Bien</td> <td>Research Psychologist</td> <td>DNB NINCDS</td> </tr> <tr> <td>J. D. Pomeroy</td> <td>Systems Analyst</td> <td>DNB NINCDS</td> </tr> </table>			PI: S. H. Broman	Acting Chief, MRLDS	DNB NINCDS	Other: E. C. Bien	Research Psychologist	DNB NINCDS	J. D. Pomeroy	Systems Analyst	DNB NINCDS
PI: S. H. Broman	Acting Chief, MRLDS	DNB NINCDS									
Other: E. C. Bien	Research Psychologist	DNB NINCDS									
J. D. Pomeroy	Systems Analyst	DNB NINCDS									
COOPERATING UNITS (if any) Dr. Peter Shaughnessy, University of Colorado Medical Center											
LAB/BRANCH Developmental Neurology Branch											
SECTION Mental Retardation and Learning Disorders Section											
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205											
TOTAL MANYEARS: .7	PROFESSIONAL: .5	OTHER: .2									
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS											
SUMMARY OF WORK (200 words or less - underline keywords) <p>The purpose of this study was to identify early behavioral, physical and familial characteristics of children with a significant discrepancy between intellectual ability and school achievement. <u>Low achievers</u>, followed from the prenatal period to age 7, were compared with their IQ-matched academically successful controls on prospectively ascertained indices of cognitive and physical development and family environment. Cognitive deficits and behavioral deviations in the preschool period were associated with low achievement at age 7. <u>Socio-economic status</u> (SES) and <u>family structure</u> were better predictors of low achievement than were indices of physical development or medical status.</p> <p>Low achievers were born into low SES, large families and were primarily male. As preschoolers, they had difficulties with verbal tasks and relatively low IQ scores. At age 7, signs of deviant behavior, verbal and non-verbal cognitive deficits, and neurological soft signs were present. Hyperactive low achievers had an increased frequency of obstetrical complications.</p>											

Project Description:

Objectives: Children with normal intelligence and poor school performance, particularly in reading, present significant problems in etiology and the development of effective remedial techniques. The accurate identification of precursors of problems in learning will facilitate prevention, early diagnosis and remediation. The objectives of this study are to determine the association between learning disorders at age seven and the following classes of variables:

1) Biological factors

- a) Complications of pregnancy and delivery
- b) Adverse neonatal conditions
- c) Neurological and general medical status at one and seven years
- d) Childhood diseases and accidents
- e) Physical growth rates

2) Socio-environmental factors

- a) Socioeconomic status of family
- b) Parental education
- c) Maternal intelligence level
- d) Family size and composition

3) Familial factors: occurrence of learning disorders in siblings

4) Cognitive and behavioral factors

- a) Psychomotor development in infancy
- b) IQ scores, motor development, and behavioral characteristics at age four
- c) IQ scores, conceptual and visual-motor development, and behavioral characteristics at age seven

Method: A child was defined as having a learning disorder if he or she had an IQ of 90 or above on the Weschler Intelligence Scale for Children and was more than one year below grade placement in reading or spelling on the Wide Range Achievement Test. This group of low achievers were compared with IQ-matched academically successful controls in order to identify early developmental patterns and concurrent cognitive and physical characteristics. Comparisons were made within ethnic group. Predictor variables were first screened individually. The significant ones were then entered into multivariate analyses.

Major Findings: (1) children with IQs of 90 or above and below average achievement test scores in reading or spelling were found to make up approximately 3% of the large unselected population of the Collaborative Perinatal Project, a proportion that agrees with the lower limit of most

estimates of prevalence of "learning disabilities"; (2) low achievers were born into low SES, large families and were primarily male. In the preschool period, they performed less well on verbal tasks and had relatively low IQ scores. At age 7, their school problems were accompanied by signs of deviant behavior, non-verbal as well as verbal cognitive deficits, presence of neurological soft signs, and other signs of physical impairment, particularly among blacks; (3) hyperactivity among low achievers was related to obstetrical complications, and past reproductive problems. Less maternal education was a characteristic of the white subgroup. At age 7, hyperactive low achievers were rated as highly impulsive, as having generalized behavioral deficits, and motor abnormalities.

Proposed Course: A monograph reporting on these data is in preparation.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02109-06 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Comprehensive Analysis of the NCPP Data on Congenital Malformations		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div> PI: N.C. Myrianthopoulos OTHER: A.F. Naylor </div> <div> Research Geneticist Research Geneticist </div> <div> DNB NINCDS DNB NINCDS </div> </div>		
COOPERATING UNITS (if any) C.S. Chung, Univ. of Hawaii; H. Lubs and M.L. Lubs, Univ. of Miami, Fla.; J. Frias, Univ. of Florida; M. Melnick, Univ. of Southern California, Los Angeles; P. Koslowe, Johns Hopkins Univ., Baltimore.		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 5.00	PROFESSIONAL: 4.00	OTHER: 1.00
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) This is a long-term project to study the epidemiologic characteristics of <u>congenital malformations</u> in <u>singletons</u> and <u>twins</u> ; to assess and interpret the influence of <u>maternal</u> , <u>socioeconomic</u> , <u>neonatal</u> , <u>medical</u> and other environmental factors on the occurrence of congenital mal- formations; to determine the <u>risk of familial occurrence</u> and to elucidate the role of <u>genetic factors</u> and the mode of inheritance of certain malformations; to determine the severity and <u>clinical</u> <u>significance</u> of congenital malformations and their associations with <u>neurological</u> , <u>psychological</u> and <u>sensory handicaps</u> ; and to assess the <u>long-range effects</u> of malformations on <u>survival</u> , <u>growth</u> and <u>development</u> .		

Project Description:

Objectives: This is a long-term project to study the epidemiologic characteristics of congenital malformations in singletons and twins; to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on the occurrence of congenital malformations; to determine the risk of familial occurrence and to elucidate the role of genetic factors and the mode of inheritance of certain malformations; to determine the severity and clinical significance of congenital malformations and their associations with neurological, psychological and sensory handicaps; and to assess the long-range effects of malformations on survival, growth and development.

Methodology: A congenital malformation is defined as a gross physical or anatomical developmental anomaly which was present at birth or was detected during the first year of life. Malformations have been classified into major and minor categories on the basis of their severity, threat to life and cosmetic significance.

The analysis is divided in 11 parts, and for each appropriate epidemiologic and statistical methods are being employed. In addition, in-depth studies of specific malformations or group of malformations are performed.

Current status and major findings:

I. Epidemiology of congenital malformations in singletons.

This part has been completed. About 15 percent of single-born children had one or more malformations. Half of the malformations were major. Only about a third of malformations observed during the first year of life were diagnosed at birth. Except for three minor malformations which were more frequent among blacks, there were no significant differences in malformation incidences between blacks and whites.

A report of this part has been published.

II. Epidemiology of congenital malformations in twins.

This part has been completed. Twins have significantly more major and minor malformations than singletons but the difference is wholly contributed by monozygotic (MZ) twins. The incidence of malformations in dizygotic (DZ) twins is the same as that in singletons. Monoamniotic twins have more malformations than diamniotic twins. Concordance rates are significantly higher among MZ than among DZ twins for all malformation categories but among specific malformations only those of the musculoskeletal system show significant differences.

A report of this part has been published.

III. A study of the effects of medical, genetic and socioeconomic factors in the occurrence of congenital malformations.

This part has been completed. Multiple birth, pregnancy complications (mostly through hydramnios) and male birth were positively correlated with increased risk in major malformations, whereas maternal weight gain was negatively correlated with major malformations. Maternal diabetes during pregnancy was significantly correlated with single or multiple major malformations.

Over one-third of children of chronic alcoholic mothers show a constellation of developmental deficits and clinical symptoms known as the "fetal alcohol syndrome". An analysis of malformations in children of mothers who took dilantin during pregnancy shows that 11% of these children show a constellation of developmental deficits and clinical symptoms consistent with the "fetal hydantoin syndrome".

Reports of this part have been published.

IV. Special analysis of the effects of diabetes in the mother on the occurrence of congenital malformations in the offspring.

This part has been completed. The risk of having a malformed child in mothers with continuous diabetes is doubled compared to that of non-diabetic mothers, with regard to major malformations and increased significantly with regard to minor malformations. The effect seems to be associated with the severity of the disease and not with the intake of insulin.

A report for this part has been published.

V. A file for genetic studies of congenital malformations.

This part has been completed. A file has been designed to derive empiric risk figures of repeating a malformation when it has once appeared in a family; to identify familial aggregations of specific malformations; and to clarify the mode of inheritance in identified familial aggregations.

The basic file to be used in genetic analyses has been considerably enlarged and has been documented. This "Family Linkage File" contains a record for each NCPP child including all information on its relationships to other NCPP children. It also combines genetic information such as family linkages, twin zygosity, etc., with important maternal and outcome variables such as malformations, minimal brain dysfunction, mental retardation, speech and hearing disorders, seizures, cerebral palsy, and visual disorders.

VI. Study of associations of ABO and Rh blood types with congenital malformations.

This study has been designed to confirm earlier suggestions of association of blood groups with congenital malformations, based on small samples.

The study has been completed. Several associations have been detected, some of which are fortuitous. The most interesting finding is a strong negative association between mother's blood group O and anencephaly. Another strong and interesting association is between pyloric stenosis and Rh incompatibility in boys. The nature of these associations should be explored in in-depth studies.

A report has been written.

VII. Study of the clinical significance of minor malformations.

VIII. Longitudinal study of development, morbidity and survival of children with malformations.

These two parts have been combined for purposes of analysis. The objective of Part VII is to establish which minor malformations are worthwhile detecting and why, and which ones can be ignored or considered as normal variants. Part VIII is a continuation of Part VII and deals with the effects of single and multiple malformations on growth and development.

All cases with multiple malformations have been carefully reviewed. Of 1,477 cases with multiple malformations, 531 were considered to have significant multiple malformations. The remaining 946 were found to have multiple minor anomalies or single malformations. Analysis of 531 cases showed that in 234 (44%) the condition was a localized error in morphogenesis (anomalad); in 154 (29%) a specific syndrome could be identified; and in 143 (26.9%) the pattern of malformation could not be identified.

A study to assess the load and achieve a classification of these malformations in terms of mortality and morbidity has been designed and is now in progress.

IX. Study of the effects of maternal factors in the production of congenital malformations.

This part has been completed. Families containing half siblings have been used in the analysis to determine maternal influences, genetic or environmental. Among informative malformations, clubfoot, congenital heart defects, umbilical and inguinal hernias, polydactyly, and café au lait spots occurred with significantly higher frequencies in half siblings than in the NCPP population. The recurrence risks of these malformations were the same in full and half siblings. While this approach cannot differentiate between genetic and environmental maternal factors, it provides clues for formulating and testing biological hypotheses.

A report for this part has been published.

X. Study of 7-year malformations.

This part will study the epidemiologic characteristics of congenital malformations in NCPP children surviving to age 7 years, make comparisons with

the 1-year malformations, and provide a basis for studies of the effects of these malformations on neurological outcome, psychological tests performance, and speech, language and hearing performance.

The study is now in progress. The 7-year malformations have been defined, identified, and classified into major and minor. New codes have been assigned for comparison with the 1-year malformations and a new file containing the 1-year and 7-year malformations has been created. Frequency distributions of the 7-year malformations have been produced by race, sex and institution.

While about 15% of children were found to have major and/or minor malformations through age 1 year, about 19% are found to have malformations through age 7 years. The increase is in eye, upper respiratory tract and mouth, and genitourinary malformations, and tumors. The upper respiratory tract and mouth malformations include a large number of tooth malformations, which constitute a new diagnostic category.

XI. Correlation of minor chromosomal variants with congenital malformations.

This part has been carried out as a contract operation with Dr. Herbert Lubs, University of Colorado, Denver, as principal investigator. The study utilizes data which have been developed by five NINCDS Collaborating Perinatal Project institutions which are currently participating in the Denver-based chromosomal study of minor variants.

About 40 "independent" significant associations were found but considering the large number of analyses performed, these are not more than would be expected by chance. The most significant associations were between strawberry/portwine hemangioma and increasing amounts of qh material; and pale Q banding heteromorphisms and skin anomalies. These results indicate that the total amount of qh or pl1 and pl3 material may be more important in the determination of developmental anomalies than any particular heteromorphism per se.

The study has been completed and a report has been written.

In-depth studies of congenital malformations

These studies have been planned as a logical extension of the original Program Plan for Comprehensive Analysis of the NCPP Data on Congenital Malformations. The specific objective is to study the epidemiologic and genetic characteristics, and natural history of specific malformations or groups of related malformations.

1. External ear malformations.

This study has been completed. The frequency of external ear malformations was 1.72% in blacks and 0.42% in whites. The frequency of familial cases was 6% in both races. Segregation analysis showed that there was a substantial number of chance isolated cases. In hereditary cases, no distinction could be made between a common recessive trait with 40% penetrance

and a rare dominant trait with 20% penetrance, or genetic heterogeneity. A most interesting finding was a significantly increased risk for hearing loss and speech abnormalities among white sporadic cases and a lesser increase among black sporadic cases.

A monograph-length report has been written and is now in press.

2. Maternal exposure to radiation and childhood tumors.

The relative risk of childhood malignancies was found to be 2.61 that of controls when mothers were exposed to radiation prior to pregnancy, and 1.5 when mothers were exposed during pregnancy. The risk was approximately the same for malignant and benign tumors. High dose examinations consistently had a higher risk than medium dose examinations.

A report has been written and is now in press.

3. Hyperthermia as a possible teratogenic agent in man.

The offspring of pregnancies exposed to high fever during the first trimester did not show significant differences from controls with regard to growth deficiencies, neurologic abnormalities or dysmorphic features. Incremental increase in fever height was negatively correlated with Binet scores but other variables such as socioeconomic status and etiologic agent could not be eliminated as alternative explanations for this finding.

A report has been written and is now in press.

4. Neural tube defects

This study will attempt to gain insight into the etiology of neural tube defects by comparing the distribution and behavior of a large number of pre- and perinatal factors in patients and controls. Epidemiologic and genetic analysis is in progress.

5. Microcephaly

This study will define measurement and clinical microcephaly, and the relation between the two; and investigate those pre- and perinatal variables which may be significant in the occurrence of microcephaly. Norms for head size by body length at 1 and 7 years have been derived, and analysis is in progress.

6. Pyloric stenosis

This study will examine possible etiologic mechanisms of pyloric stenosis by comparing the distribution and behavior of pre- and perinatal variables in patients and controls. The NCPP sample will be augmented by addition of cases ascertained in the Baltimore area.

The study is in progress.

Publications:

Myrianthopoulos, N.C.: An approach to the investigation of maternal factors in congenital malformations. In, Chung, C.S. and Morton N.E. (Eds.): Genetic Epidemiology. New York, Academic Press, pp. 363-379, 1978.

Myrianthopoulos, N.C., (Ed.): Recent Advances in the Developmental Biology of Central Nervous System Malformations. New York, Alan R. Liss, 1979.

Myrianthopoulos, N.C.: Our load of central nervous system malformations. In, N.C. Myrianthopoulos (Ed.): Recent Advances in the Developmental Biology of Central Nervous System Malformations, New York, Alan R. Liss, 1979, pp. 1-18.

Myrianthopoulos, N.C.: Summary and synthesis. In, N.C. Myrianthopoulos (Ed.): Recent Advances in the Developmental Biology of Central Nervous System Malformations, New York, Alan R. Liss, 1979, pp. 117-124.

Lubs, H.A., Patil, S.R., Kimberling, W.J., Brown, J., Cohen, M., Gerald, P.S., Hecht, F., Moorhead, P., Myrianthopoulos, N.C. and Summit, R.L.: Chromosomal abnormalities ascertained in the Collaborative Perinatal survey of 7- and 8-year old children. Birth Defects: Orig. Art. Series, Vol. XV, No. 1, pp. 191-202, 1979.

Melnick, M. and Myrianthopoulos, N.C.: External Ear Malformations: Epidemiology, Genetics and Natural History. New York, Alan R. Liss, in press.

Shiono, P.H., Chung, C.S. and Myrianthopoulos, N.C.: Maternal exposure to diagnostic radiation and childhood neoplasia. J. Nat. Cancer Inst., in press.

Clarren, S.K., Smith, D.W., Harvey, M.A.S., Ward, R.H. and Myrianthopoulos, N.C.: Hyperthermia -- a prospective evaluation of a possible teratogenic agent in man. J. Pediat., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02112-06 DNB
PERIOD COVERED October 1, 1978 through September 20, 1979		
TITLE OF PROJECT (80 characters or less) Neonatal Hyperbilirubinemia		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between; margin-top: 20px;"> PI: J. S. Drage Chief DNB, NINCDS </div>		
COOPERATING UNITS (if any) P. C. Scheidt, Division Biological Effects, BRH, FDA J. B. Hardy, The Johns Hopkins University E. D. Mellits, The Johns Hopkins University		
LAB/BRANCH Developmental Neurology Branch		
SECTION Office of the Chief		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.10	PROFESSIONAL: 0.05	OTHER: 0.05
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p> The <u>neonatal hyperbilirubinemia</u> study has been designed to assess the relationship of <u>intermediate levels</u> of serum <u>bilirubin</u> on the subsequent neurological and mental development of NINCDS Collaborative Perinatal Project children. There has been increasing concern that neonatal serum bilirubin levels between <u>10-20mg%</u> may be damaging to the central nervous system, not in the classical sense of '<u>kernicterus</u>' associated with levels above 20 mg%, but rather damaging in more subtle yet clinically significant ways. <u>Neonates</u> have been studied in five <u>birthweight-gestational age</u> categories, by three socioeconomic classes, for a variety of outcome measures, including <u>mental and motor assessments</u> at age 8 months, and spectrum of <u>neurological findings</u> at age one year which will include motor performance, reflexes, tone, abnormal movements, eye findings and the over-all neurological classification of normal, suspect or abnormal. The analysis of Phase I of this study has been published. The analysis of Phase II and III which include data obtained at age <u>seven years</u> has been completed and a publication is being prepared. </p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02169 - 05 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Obstetrical Medication and Development in Infancy and Early Childhood		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: S. H. Broman Acting Chief, MRLDS DNB NINCDS		
COOPERATING UNITS (if any) Dr. Yvonne Brackbill, University of Florida Dr. Peter Shaughnessy, University of Colorado Medical Center		
LAB/BRANCH Developmental Neurology Branch		
SECTION Mental Retardation and Learning Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .08	PROFESSIONAL: .07	OTHER: .01
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this study was to identify independent associations between medication given during labor and delivery and <u>development in the offspring</u> . Items from pediatric and psychomotor examinations in the first year were analysed in a cohort of normal births. Infants of women given <u>inhalant anesthetics</u> had increased frequencies of palpable liver and spleen, and <u>deficits in motor development</u> as compared with infants of women given regional anesthetics. Relationships between obstetrical medication and later physical and cognitive development in this cohort are also being analysed.		

Project Description:

Objectives: The purpose of this study was to identify independent associations between medication given during labor and delivery and development in the offspring. Items from pediatric and psychomotor examinations in the first year were analysed in a cohort of normal births. Infants of women given inhalant anesthetics had increased frequencies of palpable liver and spleen, and deficits in motor development as compared with infants of women given regional anesthetics. Relationships between obstetrical medication and later physical and cognitive development in this cohort are also being analysed.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02171-05 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Compendium of Heritable Disorders of the Nervous System		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: N.C. Myrianthopoulos Research Geneticist DNB NINCDS		
COOPERATING UNITS (if any) None		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.10	PROFESSIONAL: 0.05	OTHER: 0.05
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purpose is to prepare a comprehensive list of all known <u>heritable disorders of the nervous system</u> , including disorders and <u>malformation syndromes</u> which, though not primarily neurological, have neurological involvement.		

Project Description:

Objectives: To prepare a comprehensive list of all known heritable disorders of the nervous system, including disorders and malformation syndromes which, though not primarily neurological, have neurological involvement.

Methods employed: Sources for the compendium are published reports in the past and current literature containing convincing evidence of familial occurrence.

Current status: Recent additions to and deletion from the list have brought the number of neurological disorders to about 950. These have been classified into 23 nosological categories, including malformations, spinal atrophies, ataxias, demyelinating disorders, epilepsies, metabolic disorders, neuromuscular disorders, neoplasms and vascular disorders, mental retardation, syndromes, and others. The list is constantly being revised as new information becomes available.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02234-04 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Febrile seizures study		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div> PI: K.B. Nelson PI: J.H. Ellenberg </div> <div> Pediatric Neurologist Mathematical Statistician </div> <div> DNB NINCDS OBE NINCDS </div> </div>		
COOPERATING UNITS (if any) None		
LAB/BRANCH Developmental Neurology Branch		
SECTION Section on Cerebral Palsy and Other Motor Disorders		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.6	PROFESSIONAL: 0.4	OTHER: 0.2
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <p>The aim of this study is to evaluate the prevalence and prognosis of <u>febrile seizures</u>, which is the most common <u>convulsive disorder</u> in any age group. Because it has an established base population, the NINCDS Collaborative Perinatal Project has the denominator data for a quantitative statement of risks. As these were prospectively documented early examinations, this study could include information on neurological status of children before any seizure.</p> <p>An initial report dealt with the likelihood of development of chronic <u>epilepsy</u> in children who have experienced febrile seizures. A subsequent study indicates that <u>intellectual deficit</u> and <u>early learning disorder</u> are not more frequent in children with febrile seizures only. Neither death nor hemiparesis resulted from febrile seizures in this population.</p>		

Project Description: Children in the population of the NINCDS Collaborative Project who experienced febrile seizures were identified, and their seizure histories and subsequent histories examined.

Objectives: To evaluate the prevalence, associated conditions, and prognosis of this extremely common convulsive disorder. Quantification of the risks associated with febrile seizures is necessary for rational decision-making as to therapy.

Methodology: Information abstracted from the records of children with febrile seizures was used to create a tape for data analysis on a time-share system in the Office of Biometry and Epidemiology. Clinical characteristics of children with febrile seizures, and other seizure experience by the age of seven years, as well as results of intelligence testing at seven years, were examined. Sibling controls of children with febrile seizures were evaluated.

Results: Of 1821 children with febrile seizures in the Collaborative Project population, 1706 were followed to the age of seven years. Two per cent had become epileptic by the age of seven, and another one per cent had had at least one afebrile seizure not meeting the definition of epilepsy employed. Race, sex, birthweight and Apgar score were not significant predictors of epilepsy, but clinical features of the seizures, abnormal neurological status prior to the first seizure, and afebrile seizure disorders in the immediate family increase the risk of epilepsy in a child who has had a febrile seizure.

Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ, or an increased vulnerability to early learning disorder. There were no deaths and no acquired motor defects associated with febrile seizures in this series.

Predictors of recurrence, and further refinement of the relationships of characteristics of the child and types of febrile seizures to the risk of subsequent convulsive disorders have been presented. Current activities on this topic include a proposed survey and consensus meeting on the management of children with febrile seizures.

Significance: Three to four percent of children experience at least one febrile seizure. This is the most common seizure disorder in any age group, and one of the most common acute problems in child neurology. Considerable disagreement as to optimal medical management exists, and it has been our objective to supply clinically useful information as to the spectrum of risks associated with febrile seizures, as a component in therapeutic decision making.

Honors and Awards: Public Health Service Special Recognition Award to Dr. Nelson, 1977

Project No. Z01 NS 02234-04 DNB

Public Health Service Special Recognition Award to
Dr. Ellenberg, 1978

Publications: Nelson, K.B. and Ellenberg, J.H.: Predictors of epilepsy in children who have experienced febrile seizures. New Eng. J. Med. 295: 1029-1033, 1976.

Nelson, K.B.: Febrile Seizures. In Swaiman, K. and Wright, F. (Eds.): The Practice of Pediatric Neurology. St. Louis, C.V. Mosby Co., 2nd edition, 1980, in press.

Nelson, K.B.: Febrile seizures. In Moss (Ed.): Pediatrics Update: Reviews for physicians. New York City, Elsevier, 1980 edition, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02332-02 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Analysis of NCPP Twin Data		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-around; margin-top: 100px;"> <div>PI: N.C. Myrianthopoulos</div> <div>Research Geneticist</div> <div>DNB NINCDS</div> </div>		
COOPERATING UNITS (if any) NHLBI; M. Melnick, University of Southern California, Los Angeles		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: <div style="text-align: center;">1.00</div>	PROFESSIONAL: <div style="text-align: center;">0.80</div>	OTHER: <div style="text-align: center;">0.20</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p style="margin-top: 50px;"> This is a secondary area within the program plan for analysis of NCPP data. The objectives of the project are to assess and interpret the influence of <u>maternal</u>, <u>socioeconomic</u>, <u>neonatal</u>, <u>medical</u> and other environmental factors on <u>survival</u>, <u>growth</u> and <u>development</u>, and on <u>abnormal outcome</u> of twins. </p>		

Project Description:

Objectives: The objective of the project is to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of twins.

Methodology: Twins have been classified into monozygotic (MZ) and dizygotic (DZ); and MZ twins into monochorionic (MC) and dichorionic (DC). Comparisons between and among these groups, including singletons, will be made using concordance, correlation and heritability statistics.

Current status and major findings: Studies of the effects of chorion type on normal and abnormal variation showed that chorion type has no effect on and cannot explain the higher frequency of congenital malformations in MZ twins. Likewise, chorion type has no effect on head circumference, height, and right-left asymmetry. Studies involving 7-year IQ scores showed that in white MZ twins but not in blacks there is greater within pair mean square for DC than MC twins, suggesting that in white twins DC placentas are of greater influence than the similarity or dissimilarity of genomes with regard to in-trapair IQ development. Studies involving blood pressure have shown significant genetic variability for diastolic blood pressure in twins with a heritability estimate of 0.53. Systolic blood pressure results tended in the same direction but were not significantly significant. The trends were comparable for both sexes, in blacks and whites.

Currently, the hypothesis is being tested that the higher frequency of congenital malformations in MZ twins than in DZ twins and singletons is due to a 2-hit process which disrupts the developmental genetic clock of the embryo and renders it susceptible to the action of subtle environmental agents. The frequencies of several such variables as drug intake, viral infections, febrile episodes, etc. during pregnancy of mothers of MZ twins are being compared to that of mothers of DZ twins and singletons, for agreement with predictions under the hypothesis.

Publications:

Melnick, M., Myrianthopoulos, N.C. and Christian, J.: The effects of chorion type on variation in IQ in the NCPP twin population. Am. J. Hum. Genet. 30:425-433, 1978.

Myrianthopoulos, N.C.: Congenital malformations: the contribution of twin studies. Birth Defects: Orig. Art. Series, Vol. XIV, No. 6A, pp. 151-165, 1978.

Havlik, R.J., Garrison, R.J., Katz, S.H., Ellison, R.C., Feinleib, M. and Myrianthopoulos, N.C.: Detection of genetic variance in blood pressure of seven year old twins. Am. J. Epidemiol. 109:512-516, 1979.

Melnick, M. and Myrianthopoulos, N.C.: The effects of chorion type on normal and abnormal developmental variation in monozygous twins. Am. J. Clin. Genet., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02390-01 DNB
PERIOD COVERED October 1, 1978 to September 30, 1979		
TITLE OF PROJECT (80 characters or less) Huntington's Chorea Twin Study		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> PI: N.C. Myrianthopoulos OTHER: A. Williams </div> <div style="width: 30%;"> Research Geneticist Visiting Associate </div> <div style="width: 30%;"> DNB, NINCDS ET, NINCDS </div> </div>		
COOPERATING UNITS (if any) ET, NINCDS; E. Roberts, City of Hope Medical Center, Duarte, Calif.; A. Butterfield, Univ. of Kentucky, Lexington		
LAB/BRANCH Developmental Neurology Branch		
SECTION Birth Defects and Genetic Disorders Section		
INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.75	PROFESSIONAL: 0.50	OTHER: 0.25
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS </div> <div> <input checked="" type="checkbox"/> (b) HUMAN TISSUES </div> <div> <input type="checkbox"/> (c) NEITHER </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div> <input checked="" type="checkbox"/> (a1) MINORS </div> <div> <input checked="" type="checkbox"/> (a2) INTERVIEWS </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <div style="text-align: center; padding: 10px;"> <p>Using the <u>twin method</u>, this study will investigate <u>genetic</u> and <u>environmental factors</u> which may be responsible for the considerable <u>epidemiologic</u> and <u>clinical variability</u> in <u>Huntington's chorea</u>, and determine the nature of <u>gene-environment interaction</u> in this disease.</p> </div>		

Project Description:

Objectives: The objectives of this study are to investigate and identify those genetic and environmental factors which may be responsible for the considerable variability in age of onset, behavioral manifestations, clinical features, and biochemical findings of Huntington's chorea, and to determine the nature of gene-environmental interaction in this disease.

Methodology: The cooperation of monozygotic (MZ) and dizygotic (DZ) twins, one or both of whom are affected, will be secured through voluntary agencies. The twins will be admitted to the Clinical Center of the NIH for observation and study. MZ and DZ twins will be compared with regard to a number of epidemiologic, clinical and biochemical variables, including family history, age of onset, clinical findings, neurotransmitter levels, fibroblast growth rate, and red cell spin resonance.

Current status: To date 10 pairs of twins have volunteered their cooperation. One pair has been admitted to the Clinical Center and studied.

Publications: None

ANNUAL REPORT

October 1, 1978 through September 30, 1979

Stroke and Trauma Program

National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
October 1, 1978 -- September 30, 1979

Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke

INTRODUCTION

The Stroke and Trauma Program of the NINCDS is responsible for research and related training and technical consensus activities relevant to the cerebrovascular disorders, head and spinal cord injury, neural plasticity and regeneration, and CNS neoplasms. It also serves as an Institute focal point for research on positron emission tomography (PET), psychosurgery, and for chronic pain including headache, backache and manipulative therapy. Fiscal Year 1979 was characterized by the launching of new initiatives in several of these areas (e.g., comprehensive CNS trauma centers, PET program projects, research on chronic pain, controlled clinical trial of steroids in spinal cord injury); the planning of new initiatives to be implemented in FY 1980 (exploration of the needs in CNS neoplastic research through conferences, with the probable funding through research grants of a program in this field, establishment of a Joint Commission on Psychosurgery, establishment of an M.D.-M.S. research training award program); the maintenance of previously initiated research and training activities of high program priority and scientific excellence; and the discontinuation of research awards of poor productivity.

Stroke and Trauma Program areas of responsibility include the clinical entities of highest incidence and prevalence, and of severest morbidity and greatest mortality of any of the neurological disorders. Because of this, high priority is given to clinical investigations of pathogenesis, prevention, diagnosis and therapy. In addition, usually by contract, the development and dissemination of research analyses and of technical consensus are integral parts of the program's research and information initiatives. As a foundation for these clinically oriented research and evaluative activities, the program provides support for basic research relevant to the clinical areas of its responsibility. The several administrative instruments of program support (research project grants, program-project grants, clinical research center grants, cooperative trials, research contracts and service contracts) are all used as necessary and appropriate to accomplish research objectives. Because of the known shortage of skilled clinical investigators in each of the areas of program responsibility, emphasis has been given to the recruitment and development of additional investigators utilizing the institutional fellowship and teacher-investigator award mechanisms.

Thus, with the funds and other resources made available to it, the NINCDS Stroke and Trauma Program has served as the Institute focal point for the planning and operation of research and related activities in its assigned areas of responsibility. Because of limited resources, Fiscal Year 1979 was characterized by a reevaluation of program goals and objectives, the continuation of a broad-based but limited program in each of its areas of responsibility, and the initiation of a few new targeted efforts in research areas of the highest priority.

I. STROKE

The principal instrument for the support of research on cerebrovascular disease is the clinical research center grant. Currently there are twelve centers devoted to research on the natural history, diagnosis, treatment, and pathophysiology of cerebrovascular disease. Ancillary benefits derived from these centers are the training of young investigators in clinical and basic research and the stimulation of a higher level of interest in cerebrovascular disease throughout the community.

A discussion of some of the current research projects in these centers follows:

The group at the University of Alabama, in Birmingham, under the direction of Dr. James Halsey is developing and implementing methods of studying important physiological mechanisms in conjunction with highly sophisticated mathematical modeling and computer simulation. The hypothesis is that the process of evaluation of cerebral infarction and ischemia is extremely complex involving many physiologic processes which interact with each other and in turn trigger other reactions.

Since the ultimate goal is improved treatment of the stroke patient at the bedside, it is necessary to make interpretations for the human brain based on animal models which differ in important respects as regards collateral circulation, physical capacity of the cranium, and neuron-glial ratio.

The computer simulation is seen as a means of making much more efficient use of experimental animals, designing appropriate experiments to answer relevant questions, and making more accurate interpretations applicable to the human situation.

Initial progress has now been made with programs to monitor the processes of tissue lactate accumulation, together with changes in bicarbonate, hydrogen ion, and PCO_2 in simple anoxia, and total ischemia in the gerbil model. Further work with these programs is now underway involving different assumptions about glucose supply, the shift from aerobic to anaerobic glycolysis, and resting metabolic rate. Additional variables will be sequentially introduced to account for changes in microcirculation, oxygen diffusion, potassium flux, neuronal activity, and other relevant variables.

This close link of pathophysiologic experiments with computer based systems analysis is relatively unique among the centers.

Drs. Pulsinelli, Brierley, and Levy from Cornell University Medical College presented an abstract at the Cerebrovascular Clinical Research Center Workshop describing studies of global cerebral ischemia in a rat model which they have developed. The procedure used allows the animal to survive and will produce ischemia during the wakeful state. The technique consists of coagulating the vertebral arteries and 24 hours later temporarily occluding the carotid arteries of the unrestrained animal. Occlusion only lasts one-half hour after which the surviving animals undergo a predictable brain injury which gradually increases in intensity over a 24 hour period. The data suggest that some post-ischemic mechanism continues to jeopardize neurons and that this process may

continue for many hours following a transient episode of cerebral ischemia. If these data demonstrating a time lag between cerebral ischemia and completion of neuronal death are also valid for human stroke, then clinicians may have some lead time to initiate therapies to reduce or minimize brain damage.

The team at Massachusetts General Hospital under the direction of Dr. Juan Taveras has been developing non-invasive approaches to monitoring cerebral blood flow. They now have a fully operative Xenon inhalation laboratory tied to an on-line computer facility and a computer program which can yield rapid results in up to 12 regions of the brain on each side.

Routine clinical application of this non-invasive approach has begun and data are already accumulating in stroke patients.

Another important investigation proceeding simultaneously has been a thorough exploration of the utility of cyclotron produced, short lived isotopes, all of them positron emitters, first in the measurement of regional cerebral blood flow, and secondly in the investigation of regional metabolic parameters.

Dr. Taveras and his colleagues have succeeded in developing a relatively non-invasive approach to measuring regional cerebral blood flow by inhalation of O_2 and CO_2 tagged with $^{15}O_2$. It is also possible, by the same approach, simultaneously to measure regional oxygen consumption by utilizing the ratio of the counts obtained with inhaled $^{15}O_2$ (oxyhemoglobin) to those obtained in the same regions with $C^{15}O_2$ (incorporated in water almost instantly). Thus, the water, being freely diffusible, is an indicator of blood flow, whereas the oxyhemoglobin is an indicator of oxygen uptake by the tissues.

In the past few months the use of two-dimensional positron studies in demonstrating regional cerebral circulation and metabolism has been systematically evaluated, quantitation of these data has been attempted and the production of three-dimensional images has been initiated. Compounds used were ^{13}N labeled NH_3 , ^{15}O labeled O_2 , CO_2 and CO , and ^{11}C labeled glucose. Seventy five patients and subjects were studied, fifty-five with the two-dimensional camera the fifteen with the three-dimensional. For blood flow (using $^{13}NH_3$ and $C^{15}O_2$) and oxygen uptake ($^{15}O_2$) the normal scintigrams were established. Disturbances in CBF and/or metabolism were found in patients with large, obvious infarcts, tumors and AVM's seen on arteriography and CT scan, but also in acute stroke patients in whom the arteriogram and CT scan were negative.

Tracer studies at Washington University in St. Louis have focused on the development of techniques to measure tissue substrate utilization, chemical composition, and blood volume using positron emission tomography (PET) and ^{11}C -glucose, ^{11}C -carbon dioxide, and ^{11}C -carbon monoxide, respectively. In addition, Dr. Raichle and colleagues have examined the behavior of ^{13}N -ammonia as a tracer for the measurement of cerebral blood flow.

The role of erythrocyte carbonic anhydrase is being investigated in rhesus monkeys. This compound appears to perform a critical role in coordinating the hydration of metabolically produced carbon dioxide and the release of oxygen from hemoglobin to the tissue. Inhibition of carbonic anhydrase

produces a significant reduction in cerebral oxygen utilization. Supplementation of carbonic anhydrase activity by the addition of the enzyme to plasma augments cerebral oxygen utilization. This critical dependence of brain oxidative metabolism on intravascular factors concerned with the release of oxygen to the tissue has not heretofore been appreciated. As an extension of this work, Dr. Raichle has developed a technique for the measurement of tissue oxygen content using a dual tracer technique employing ^{15}O labeled water and ^{15}O labeled oxyhemoglobin. The technique, which provides a value for the partition for oxygen between blood and tissue, allows for an accurate measurement of tissue oxygen content. The results to date demonstrate a small, but appreciable pool of oxygen within brain tissue, which can be varied in size by the manipulation of erythrocyte carbonic anhydrase. Studies over the next year will continue to explore the relationships involved in this unique system, as well as factors such as catecholamines which may influence the activity of carbonic anhydrase and hence brain oxidative metabolism.

The rapid irreversibility of neural survival after ischemic insult may not be as severe or complete if ways can be found to control the various biochemical and physiological complications and suppress the cellular energy expenditure in the face of energy crisis.

Dr. Peritz Scheinberg and his associates at the University of Miami have developed an embolic stroke rat model to investigate the hypothesis that cerebral ischemia is an evolving process and that there are distinct well defined stages which they are attempting to characterize. Several variables can be measured in the same brain region by means of highly sophisticated topographic methods. It is possible to correlate on a regional basis in the same brain results of measurements of ATP, NADH, pH, and glucose utilization. Since the mechanism of tissue injury and protection are different in the various stages of ischemic brain injury, they suggest that rational therapy of acute occlusive cerebral vascular disease must be systematized in a "Time Specific" fashion.

The development of the ^{18}F 2-fluorodeoxyglucose technique for the measurement of local cerebral glucose metabolism in man by the use of positron emission tomography has been a major accomplishment of the Center at the University of Pennsylvania. This technique has made it possible for the first time to measure changes in glucose utilization in various structures in the brain of man in a quantitative fashion. It has already been used in various pathologic conditions such as stroke, seizure disorders and mental disorders and has provided valuable new information which may further our understanding of these conditions and aid in the evaluation of various therapeutic modalities. This technique which has also been used to map neural pathways in man may provide us with valuable new information concerning the organization of functional activity in the brain.

Dr. Martin Reivich reported on this work at the Ninth International Salzberg Conference on Cerebrovascular Disease.

A new Program Project Grant was awarded to the University of Pennsylvania this past year to enable Dr. Reivich and his colleagues to set up a tomographic

scanner with optimal resolution capability and to provide with the aid of the Nuclear Physics Department for on-site generation of short lived radiopharmaceuticals. The most immediately important among these will be ^{11}C deoxyglucose.

The use of this radiopharmaceutical will allow a second measurement of local cerebral glucose utilization within two hours because of its short half life.

Ultrasound as a diagnostic tool for evaluating cerebrovascular disease is of interest to many of the Centers.

An ultrasound B-scanner developed jointly by the Mayo Foundation and Stanford Research Institute has been under clinical trial at Mayo since 1975. High resolution and real-time capacity of the instrument coupled with the safety, speed, and reproducibility of the examination technique have made it possible to obtain good images of the carotid bifurcation in the majority of patients, some of whom have undergone subsequent angiography. Initial, favorable impressions prompted a prospective comparative study between carotid B-scanning and carotid angiography.

It was found that about one-third of the lesions are accurately identified in regard to extent and location as compared to the angiogram. About one-third are within one grade of that identified by angiography and approximately one-third do not correlate well with angiography.

At the present stage of development and testing, these investigators believe that real-time ultrasound scanning of the carotid arteries represents a promising adjunct to clinical practice but so far there is no indication that it will substitute for the need for angiography in most patients being considered for surgical treatment of ischemic cerebrovascular disease.

Two reports on ultrasound technology from Dr. James Toole's Center at Bowman Gray Medical School were presented at the Cerebrovascular Center workshop. A 5 MHz dual linear phased array system has been used in studying the external extracranial carotid arteries in non human primates with carotid artery diameters less than 2 mm and in human subjects.

Improvements in the ultrasound system and techniques have also resulted in significantly improved images of intracranial arteries.

A major decline in the incidence of stroke was reported from the Center at the Mayo Clinic. For every 100 first episodes of stroke that occurred per unit of population in Rochester, Minnesota during the period 1945-49, only 55 occurred in the period 1970-74. Although the decline was present in both sexes and in all age groups, the reduction in rates was more pronounced in the elderly. There was no major change in age of onset.

The validity of the data is enhanced by an overall autopsy rate of 58 percent among Rochester residents during the study period, a high level of involvement by members of the Department of Neurology at the Mayo Clinic in the diagnosis and management of stroke, and a standard quantifiable clinical examination used for all patients with any neurologic disorder. From January 1, 1945, to

December 31, 1974, 1854 new cases of stroke, occurring during 1.2 million person-years of observations in residents of Rochester, were recorded in the medical records of the Mayo Clinic and all other affiliated sources.

Prostaglandins are reported to play a major role in the etiology of cerebral vasospasm following subarachnoid hemorrhage. Sources of these prostaglandins may be blood, cerebral blood vessels and brain tissue. In order to establish a profile of the prostaglandins synthesized by cerebral blood vessels and brain tissue, the capacity of these tissues to synthesize prostaglandins from 1-¹⁴C arachidonic acid in vitro has been studied by Dr. James Robertson and colleagues at the University of Tennessee. They found that the major prostaglandins synthesized were those which are spasmogenic to cerebral vessels and have postulated that the vasospasm of cerebral blood vessels following subarachnoid hemorrhage may be due to the release of these lipids.

Animal experiments are now underway to determine whether known inhibitors of prostaglandin synthesis will reduce the incidence of SAH in dogs.

Another approach to the study of subarachnoid hemorrhage is that of Dr. Erland Nelson at the University of Maryland. He and his associates are examining in animal models the structural alterations of arteries undergoing vasospasm. Results indicate that an arterial stenosis is virtually always associated with varying degrees of structural damage, platelet aggregation or thrombosis. Initial studies of the basilar artery have been extended to include the thoracic aorta, and the carotid, vertebral, renal, and coronary arteries. A study to test the hypothesis that such arterial injury is the site of embolization is now in progress.

At the Duke University Center progress has been made by Drs. Heyman and Wilkinson in enlarging a computerized information system for the study of TIA. The relationship of the neurologic, arteriographic and systemic manifestations of transient cerebral ischemia (TIA) to the outcome of medical or surgical therapy of this illness is being investigated. More than 300 patients with TIA have been entered into this data bank thus far, of whom only 10 patients have been lost to follow-up. Follow-up observations are being made at regular intervals by clinic visits, phone calls and letters to the patients and their physicians.

During the past year, a survey was initiated to determine the morbidity and mortality from cerebrovascular disease among 17,000 men and women living in a southern California retirement community. The purpose of this survey is to determine whether the occurrence of stroke in this population can be related to information on the precursors of cerebrovascular disease which was obtained from questionnaires completed by a large segment of this community in 1976. Analyses of this material should be of value in elucidating the natural history of transient ischemic disease as well as other risk factors for stroke. Useful information will also be obtained from this survey in regard to the value of community-wide screening programs for the prevention of stroke. ,

Dr. James N. Davis who has replaced Dr. Albert Heyman as Principal Investigator of this Cerebrovascular Research Center is continuing the ongoing research but

is also introducing a long range goal of studying the recovery of function after stroke. In the future the Center will bring together basic and clinical research activities which are focused on understanding the biological basis for recovery of function and developing rationale therapy for stroke patients.

At Baylor University noninvasive measurement of regional cerebral blood flow, neuropsychological tests, and CT scans are being compared in normal volunteers between 18-100 years of age, in subjects without brain disease but with risk factors for cerebral arteriosclerosis (hypertension, diabetes, hyperlipidemia) and in patients with cerebrovascular disorders including: transient ischemic attacks, cerebral infarction, subarachnoid and intracranial hemorrhage, multi-infarct and related dementias, migraine and vascular headache.

Representatives from all of the Cerebrovascular Research Centers participated in a workshop sponsored by NINCDS held in Phoenix, Arizona, February 6-7, 1979. Prior to this meeting a two-day workshop was held on Non-Invasive Xenon Cerebral Blood Flow Applications. The topics discussed covered essentially all of the important clinical and methodological aspects of xenon blood flow studies.

In addition to the 12 Cerebrovascular Research Centers in the Stroke Program there are 41 active research project grants which are also focused on the natural history, diagnosis, treatment, and pathophysiology of cerebrovascular disease. Eight new projects were initiated during the past year.

As of May 25, 1979, 352 patients had been entered into the Extracranial/Intracranial Arterial Anastomosis study. The current acquisition rate is considered satisfactory. Details of study design have been further refined and data forms and operating procedures have been simplified and made more efficient.

II. SPINAL CORD INJURY

Spinal cord injury research has two main thrusts: (1) to explain secondary (and presumably reversible) reactions of the spinal cord to mechanical injury and (2) to assess the effectiveness of currently available methods of diagnosis and treatment.

At varying time intervals after spinal cord injury secondary reactions (edema, ischemia, hemorrhage) occur. Much of the present spinal cord injury research is based on the hope that a better understanding of the pathophysiology of these reactions will permit effective treatment of spinal cord injured patients and so decrease their neurologic deficits.

There are indications that some of the currently available methods of treatment of spinal cord injury may be effective in improving neurologic outcome. However, it is often difficult to say which spinal cord injured patients will benefit from which treatments, and at what time, at what dosage and for how long various treatments should be given. To answer such questions both laboratory research and controlled clinical trials are being done.

The bulk of spinal cord injury research is being done at five Spinal Cord Injury Clinical Research Centers funded by the NINCDS. These center grants have been awarded to:

1. The Medical University of South Carolina
2. New York University
3. Ohio State University
4. Yale University
5. The University of Texas at San Antonio

Highlights of the work done at these centers in the past year are:

A. Epidemiology

The Yale Spinal Cord Injury Clinical Research Center continues to collect and analyze data on all spinal cord injuries in the state of Connecticut. This will be the most complete study of spinal cord injury in a defined geographic area and will address many aspects of spinal cord injury, including causes, treatment, outcome and cost. The cases collected are divided into those treated in community hospitals versus those treated in the spinal cord injury center. This is the first study to compare specialized center treatment and community hospital treatment.

B. Pathogenesis

1. Studies of catecholamine changes in spinal cord injury have continued in several laboratories. Early suggestions from the literature that a major cause of secondary injury following spinal cord injury could be the release or accumulation of norepinephrine at the site of injury have not been confirmed. Turnover studies using tritiated tyrosine and L-DOPA have demonstrated a reduction in the activity of tyrosine hydroxylase. Also the activity of membrane-bound enzymes, dopamine

beta-hydroxylase and mitochondrial monomine oxydase, was curtailed. This resulted in an accumulation of dopamine and no change in norepinephrine concentrations. These results suggest that the change in catecholamine metabolites seen after spinal cord injury probably reflects membrane perturbations and disruption of function of membrane-bound enzymes. Thus, catecholamine alterations are felt to be a secondary phenomenon and not of etiologic significance in the development of degenerative changes following spinal cord injury.

2. Localized spinal cord trauma has been found to result in decreased blood flow throughout the entire central nervous system, with the spinal cord being more affected than the brain. The exact mechanisms are unknown but there is a suggestion that there is sequestration of blood in para-spinal, pelvic and lower extremity muscles. This could be due to an autonomic paralysis affecting vasomotor tone below the level of injury. Blood flow in the traumatized segment of the spinal cord is therefore subject to two disruptive mechanisms: the direct effect of trauma on blood vessels of the spinal cord plus the generalized fall in blood flow. The combined effects of low flow rates and presumably low perfusion pressure plus obstruction of micro-circulation could cause ischemia sufficient to produce irreversible changes in spinal cord axons.
3. Studies of edema using a rat brain model (brain rather than spinal cord because of the volume of tissue available) demonstrated that cholesterol and ascorbic acid levels were significantly lowered. However, if the animals were treated with methylprednisolone there was almost a complete prevention of the changes in cholesterol and ascorbic acid, suggesting that the protective effect of corticosteroids on central nervous system edema may be due to stabilization of cell membranes by protection of major membrane components such as cholesterol and preservation of the endogenous antioxidant, ascorbic acid.

C. Diagnosis and Treatment

1. Study of the somatosensory evoked potentials (SEP) in chronic spinal cord injured animals reveals that return of the SEP correlates with return of motor function and therefore confirms the validity of the SEP as a prognostic indicator for return of spinal cord function.
2. A double blind randomized collaborative clinical trial to study the effects of corticosteroids on spinal cord injured patients has been awarded to Yale University. This study is being carried out by all the Spinal Cord Injury Clinical Research Centers plus three other university hospitals. All eligible consenting patients are being randomly assigned to either standard or large doses of methylprednisolone. This is an important study in its own right and also because the methodology involved will serve as the basis for future studies of other methods of treatment in spinal cord injury.

3. The effects of mannitol and DMSO on animals with 400 gm-cm spinal cord injuries were compared. No improvement was seen in the animals who received mannitol following injury. In the DMSO groups seven out of twenty animals (35%) showed return of neurologic function.

In addition to the Spinal Cord Injury Clinical Research Centers there are eighteen regular research grants dealing with the spinal cord. These vary from basic studies of anatomy and physiology such as: "Pain Mechanisms after Spinal Cord Lesions," "Structure and Function of Supraspinal Pathways," and "Biomechanics of Experimental Spinal Cord Injury" to clinical studies such as: "Arachnoiditis Following Myelography."

III. HEAD INJURY

With the indication now (see Epidemiology) that intensive monitoring and vigorous treatment of head injured patients yield a decrease in mortality and morbidity, more research is being undertaken in the field of brain trauma. This includes clinical trials of methods of patient management as well as more basic studies of pathophysiology.

The Head Injury Clinical Research Centers funded by the NINCDS remain at the forefront of this research. These centers are located at:

1. Albany Medical College
2. New York University
3. The University of Pennsylvania
4. The University of Texas at Galveston
5. Virginia Commonwealth University.

Among the findings reported by these Centers in the past year are the following:

A. Epidemiology

1. In one series of 160 severely head-injured patients (reported in October 1977, Journal of Neurosurgery) a mortality rate of 30% was reported with no increase in the numbers of severely disabled or vegetative patients. This appears to represent a definite improvement when compared to other recent series of severely head-injured patients. In a series of 53 children with severe head injury (reported in May 1978, Journal of Neurosurgery) 90% made a good recovery or were moderately disabled and 8% died or were left vegetative. The high percentage of good outcomes in these series are attributed to careful monitoring and vigorous treatment. If substantiated, these figures represent the first outcome figures to justify modern technology in the treatment of head injury.
2. One of the clinical research centers is also involved in a new program of the NINCDS, the Comprehensive Central Nervous System Trauma Center Program. (See Contract Narrative "Feasibility Studies for Comprehensive Central Nervous System Trauma Centers.") One of the major efforts of

this program will be the study of the incidence, prevalence, cause, treatment and outcome of head and spinal cord injuries in defined communities.

3. Neuropsychological profiles and functional outcome levels have been obtained by several groups. In one center over 100 patients with closed head injury have been studied with detailed testing. The types and incidences of specific defects in language, perception and memory have been characterized.

B. Pathogenesis

1. Studies of cerebral blood flow in head injury are being pursued in several centers. One center, with particular expertise in this field, has demonstrated the presence of hyperemia in some patients comatose after head injury. Because of previous reports that cerebral metabolism is depressed in coma these findings of hyperemia in certain comatose patients raise a question concerning the relationship between cerebral blood flow and metabolism in this condition. Specifically, is the elevated blood flow coupled with a high cerebral metabolic rate or is there a dissociation between blood flow and metabolism such that cerebral blood flow is in excess of metabolic demand? Two distinct patterns are seen, depending on the level of blood flow. While there is little or no relationship between CBF (cerebral blood flow) and CMRO₂ (cerebral metabolic rate) when blood flow is elevated, there is a significant correlation when blood flow is decreased. Blood flow in the hyperemic cases exceeds metabolic demand by 2 to 3 times, a true "luxury perfusion."
2. One research group in studying the effects of stereotactic brain stem lesions on CMRO₂ in rats found that sequential lesions produce a different, much less severe, neurologic deficit than the same lesions placed simultaneously. These observations parallel earlier findings in cats and suggest that it is not the volume of brain tissue destroyed but the volume destroyed at a given moment which determines the development of the non-adaptive state. These experiments suggest that there is a capacity for functional plasticity in the nervous system.

C. Diagnosis and Treatment

1. In patients with diffuse brain injury, initial ICP is closely related to outcome; however, in patients with mass lesions, there is no significant correlation between initial ICP and outcome.
2. CAT scanning continues to be evaluated in head trauma. In one series those patients who had or developed bilateral lesions of increased density in the CT scan showed a higher than expected incidence of abnormal or absent motor activity. This association is of interest as there is increasing evidence that in many cases the appearance of decorticate or decerebrate posturing is an indication not of brain stem damage but of bilateral hemispheric lesions.

3. Considerable work has been done in assessing the use and reliability of evoked potentials in head injury. The ability of evoked potentials to evaluate dysfunction in specific neural systems has proved valuable in diagnosing focal deficits in comatose patients. Visual and auditory evoked potentials, recorded in comatose patients, significantly correlate with retrobulbar dysfunction and auditory dysfunctions, especially from eighth nerve damage, and were more effective than the neurologic examination in diagnosing dysfunction in these sensory systems early in the post-traumatic period. Evoked potentials have also been of use in defining the site of brain injury. Abnormal somatosensory and auditory near and far-field (brain stem) EP's recorded from comatose head injury patients with normal visual EP's suggest brain stem dysfunction more than cerebral hemispheric dysfunction. On the other hand normal auditory brain stem potentials (far-field) and abnormal auditory near-field potentials coupled with abnormal visual and somatosensory potentials suggest electrophysiologic dysfunction of the cerebral hemispheres.

In July, 1978, a grant was awarded for a Brain Edema Clinical Research Center. Studies currently under way there are:

1. Metabolic Basis of Granulocytic Brain Edema,
2. Osmotic Regulation and Neurotransmitter Metabolism in Brain Edema,
3. Pathophysiology of Brain Edema: in vivo (rat) Studies,
4. Barbiturates and Ischemic Brain Edema,
5. Neurogenic Pulmonary Edema,
6. Brain Capillary Metabolism and Function,
7. Transport Systems of the Choroid Plexus.

A special effort of the Stroke and Trauma Program, intended primarily for the use of young investigators is the Central Nervous System Trauma Research Status Report currently being compiled, with publication planned in 1980.

In addition to the research being done in the clinical research centers there are twenty regular research grants dealing with head injury. These include such research projects as "CSF Secretion: Structure and Function," "Systemic Effects of Increasing Intracranial Pressure," and "Mechanisms of Brain Dehydration with Osmotic Diuretics."

IV. CNS NEOPLASIA

The research program in CNS neoplasia remains a small one, containing at present five research grants. These grants are concerned with basic aspects of CNS neoplasia research such as: "Regulation of Brain and Tumor Phosphotransferase," "Clonal Cell Lines of the Nervous System," and "Metabolic Regulation in Glioma Cells." However, plans are presently being made for a series of symposia on neuro-oncology. The aim of the symposia will be to define those areas in CNS neoplasia that need more attention and to stimulate research in these areas.

V. NEURAL REGENERATION AND PLASTICITY

The traditional belief that the injured central nervous system is incapable of recovery has been seriously challenged in recent years by an increasing number of effective neuroscientists. It has become well recognized that the neurons and axons of the transected or traumatized spinal cord can produce sprouts that initiate the process of re-growth toward target axons. The reasons for the typical inhibition or blockage of this re-regrowth process are being investigated through the use of enzymes, grafting, use of prosthetic guides or channels, chemical and electrical growth stimulators, and other approaches.

The eventual aim of these studies--recovery of function--has not yet been achieved. However, the quantity and especially the quality of specific knowledge of the biological phenomena taking place have increased markedly within the past few years.

Research activities in regeneration and plasticity of the injured nervous system are almost all at the basic science level, as required by the present state of knowledge. However, the nature, the breadth, and the ingenuity of such research has been changing rapidly. The increased use of nerve tissue culture techniques, of immunological and genetic principles in studies of nerve grafting, and computer-assisted three-dimensional reconstruction methods of visualizing dynamic nerve processes are all contributing to a rapidly progressing and promising research field.

Regeneration and plasticity research is supported by the Stroke and Trauma Program mainly through research grants to individuals or small teams of investigators in academic medical centers. There are 76 research project grants totalling \$6.0 million. These cover a wide range of subjects. Progress is steady but, as in most basic fields, not spectacular; these studies are certainly extending and confirming the basic knowledge on which applied research, and eventually clinical application, will be based.

Research supported by Stroke and Trauma Program grants is in progress on:

- * Development and regenerative properties of embryological and neonatal nerve tissues.
- * Processes of regrowth of injured axons and reestablishment of synapses in severed nerves.
- * The chemical nature and mode of biological activity of nerve growth factors and related substances in promoting re-growth of injured nerves.
- * Axonal transport including effects of axon-sheath relationships.
- * Plastic phenomena as a means of restoration of partial function following nerve injury.

The Stroke and Trauma Program has supported by contract a single study to replicate the claims by Matinian in the USSR that through the introduction of enzymes into the lesion following cutting of the rat spinal cord, functional recovery can be achieved. The Matinian reports have not been verified. The contractor's report is in process of publication. It appears that the explanation for the Soviet unverifiable claim lies in the almost certain incomplete severance of the rat spinal cord. The contractor's results have been confirmed by separate publications by two grantees.

Among recent publications in nerve regeneration and plasticity several reports are of special interest for future major advances in practical application. These include:

Recently published work has shown that grafts of fetal rat brain tissue implanted adjacent to areas of the brain of adult rats whose control of specific motor functions had been destroyed resulted in partial restoration of the destroyed functions. These data suggest that implants may be useful in reversing deficits after specific destruction of brain tissue. An eventual possible application to the treatment of the damaged spinal cord is implied.

U.S. and Swedish investigators have shown that neurons grafted into the brain will regenerate and reinnervate damaged regions of the brain, thus proving that neurons can survive temporary loss of blood supply and that subsequent outgrowth of nerve processes can occur. In very recent work they have extended this work by showing that a variety of rat embryonic neural tissues survive grafting into the adult rat brain. After implantation, neurogenesis and differentiation continue and functional connections are formed. This work offers new excellent model systems for investigation of developmental and regenerative phenomena.

Recent research from several laboratories has strongly indicated the existence of several nerve growth factors of distinctly different chemical structures and neurogenic specificities. These nerve growth factors offer new opportunities for studying the mechanisms of neuronal development and regeneration.

The steady increase in publications in CNS regeneration and plasticity, in membership in scientific research societies concerned with this field, and in the reorientation of established neuroscience investigators to studies of CNS regeneration all point to the potential for advancement in the field of CNS regeneration.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1978 -- September 30, 1979

UNIVERSITY OF ROCHESTER (N01-NS-8-2385)

NORTH CAROLINA HEART ASSOCIATION (N01-NS-8-2386)

UNIVERSITY OF OREGON HEALTH SCIENCES CENTER (N01-NS-8-2387)

Title: Comprehensive Stroke Center

Project Directors: John H. Feibel, M.D. (Univ. of Rochester)
Paul E. Hirschauer (North Carolina Heart Assoc.)
Frank M. Yatsu, M.D. (Univ. of Oregon)

Current Level of Support: \$475,183 (Rochester)
\$555,207 (N.C. Heart)
\$752,387 (Oregon)

Objectives: The objectives of these centers are to:

- a. Conduct a program of applied clinical research in which fundamental advances are utilized in the development of specific approaches, the prevention, diagnosis and management of cerebrovascular disorders.
- b. Develop integrated and coordinated community resources to evaluate the results of research on the prevention, diagnosis, and treatment of cerebrovascular disorders.
- c. Demonstrate to physicians, other professionals and the public, by a broad public education program, the significant advances in cerebrovascular research and management.

Major Findings and Proposed Course:

1. North Carolina Heart Association

The total program is composed of two major components, treatment and prevention. The evaluation of the treatment component of the program includes comparison of patient outcomes in counties in which the program has been implemented with outcomes in counties in which the program has not yet been implemented. The total 16-county area has been divided into three groups of five to six counties each. The program has been implemented in the first group (A) without measurement of preprogram patient outcomes. In the second group (B), data is being collected without implementation of the program for a 9 to 10 month period. At the end of this period, the program will begin in group B and data collection without program operations will begin in group C. At the end of another 9 to 10 month period, the program will be implemented in the group C counties. The program will operate in all 16 counties for the final nine months of the three year contract.

Specific strategies for identifying and providing preventive services to target groups are being developed, and community resources required for effective intervention in reducing or avoiding risk factors of stroke are being organized.

2. University of Oregon Health Science Center

The Center at Oregon is organized around four projects - Education, Epidemiology and Preventive Medicine, Clinical Research, and Rehabilitation. During the past year circuit course lectures on stroke have been offered to physicians in Oregon and Idaho. A Comprehensive Stroke Center News Letter has been published and sent to all neurologists, neurosurgeons, family practitioners, and internists in the state, and circuit course lectures have been given throughout the state.

Epidemiology and Preventive Medicine: Fifteen hundred and seventy residents of the Housing Authority of Portland were screened for stroke risk factors with the results that 150 persons with asymptomatic bruits were discovered.

Clinical Research: Clinical investigations on the value of barbiturate and vasopressor therapy on stroke and studies of the asymptomatic bruit have begun. Studies on acute speech and language characteristics of stroke patients and the neuropsychological aspects of stroke are in progress.

3. University of Rochester, Rochester, New York

Monroe County, New York serves as the population base of this Center. The investigators of each of four research projects have been working to obtain the cooperation and participation of the health care establishment and to develop methods for handling the data collection and storage.

The four research projects in progress are:

1. The Decision Model for Assigning Patients to Intensive Rehabilitation
2. Family Oriented Stroke Rehabilitation Program
3. Evaluation of Community Stroke Groups
4. Community Wide Surveillance of the Incidence and Preventability of Cerebrovascular Disease.

The Center has already had an impact on the attitude behavior of health professionals toward stroke. The number of patients referred for intensive rehabilitation after stroke has increased due to the Center's staff encouragement. Hospital personnel have become more aware of the rehabilitative needs of patients and have responded by requesting in-service training and by stating their desire to hire staff (such as their own stroke nurse or occupational therapist) and obtain equipment (e.g., adaptive equipment for occupational therapy).

Significance to the NINCDS Program and Biomedical Research: The ultimate objective of the Comprehensive Stroke Program Center is that by the end of a three year period, the health status and economic situation of the population in regard to stroke and its costs will have been improved through lower incidence, higher age at initial onset, lower mortality severity and morbidity, higher level of independence and lower economic costs.

Proposed Course:

<u>CONTRACTOR</u>	<u>TERMINATION DATE</u>
University of Rochester	6/28/81
North Carolina Heart Association	5/31/81
University of Oregon Health Sciences Center	6/14/80*

*It is expected that a detailed proposal will be submitted for a third year of support.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1978 -- September 30, 1979

MAYO FOUNDATION (N01-NS-6-9033)

Title: Bibliographic Service on Cerebrovascular Disease

Contractor's Project Director: Robert G. Siekert, M.D.

Current Annual Level of Support: \$56,750

Objective: To provide an abstracting service relative to various aspects of cerebrovascular disease. Contents of 150 journals are scanned. The abstracts are published in Stroke, a Journal of Cerebrovascular Disease.

Significance to the NINCDS Program and Biomedical Research: The abstracts on cerebrovascular disease continue to be a valuable service to the health profession.

Proposed Course: This contract will terminate 5-31-80.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1978 -- September 30, 1979

YALE UNIVERSITY (N01-NS-7-2361)

Title: Feasibility Study to Develop Data Collection Instruments and
Protocols at the National Acute Spinal Cord Injury Centers

Project Director: William F. Collins, M.D.

Current Level of Support: 0

Objectives: To develop and test data collection forms to be used by all Spinal Cord Injury Clinical Research Centers. Also, to standardize, as much as possible, the methods of performing and recording the neurologic examination. Such a data collection system will permit pooling of cases and more rapid evaluation of therapy.

Major Findings: Representatives of the Spinal Cord Injury Clinical Research Centers have completed work on the data collection forms. These have been tested and found to function satisfactorily.

Significance to the NINCDS Program and Biomedical Research: This effort is of major importance to our clinical research program in spinal cord injury. The accession of spinal cord injury cases is too low in any one center to permit accumulation of data in a short enough time to assess any method of treatment. With this pooling of cases, such assessment should be possible.

Proposed Course: This contract terminated January 31, 1979. The work proposed was successfully completed. Participating institutions used common data collection forms and agreed on standardized use of terms and examination techniques. This work is now continuing through a research grant, NS 15078, titled "Methylprednisolone and Spinal Cord Trauma," awarded in February, 1979, to Yale University. This is a randomized double blind clinical trial of the use of high dosage versus low or "normal" dosage steroids in spinal cord injury. In addition to the Spinal Cord Injury Clinical Research Centers, the University of Miami, the University of Texas at Galveston, and the University of Puerto Rico, are participants.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1978 -- September 30, 1979

UNIVERSITY OF NEW MEXICO (N01-NS-5-2332)

Title: Quantitative Intracranial Pressure Measurement in Man

Project Director: A. Earl Walker, M.D.

Current Annual Level of Support: 0

Objective: To evaluate clinically a system for monitoring intracranial pressure.

Major Findings: In all, 41 transducers were implanted in 36 patients with acute head trauma, aneurysms, cerebral anoxia, brain tumors, adult hydrocephalus and pseudotumor cerebri. In patients with the latter two conditions, the ICP monitor results were used to determine whether or not a cerebrospinal fluid shunt would be of value and to evaluate the efficacy of medication.

The biggest problem with chronically implanted ICP systems continues to be base-line drift, so that long-term, accurate, absolute pressure levels are not possible without periodic calibration by intrathecal puncture. However, rapid changes in ICP (time course less than one day) were detected, and such measurements were used to assess shunt function.

Significance to Biomedical Research and to the Program of the Institute:

A system capable of detecting increases in intracranial pressure before clinical signs manifest themselves would permit better and faster treatment of patients with intracranial lesions.

Proposed Course of Contract: This contract has been terminated.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1978 -- September 30, 1979

ALBERT EINSTEIN COLLEGE OF MEDICINE (N01-NS-7-2371)
UNIVERSITY OF CALIFORNIA AT SAN DIEGO (N01-NS-7-2370)
UNIVERSITY OF MIAMI (N01-NS-7-2368)
UNIVERSITY OF MINNESOTA (N01-NS-7-2369)
UNIVERSITY OF TEXAS MEDICAL BRANCH (N01-NS-7-2372)
UNIVERSITY OF VIRGINIA (N01-NS-7-2373)

Title: Feasibility Studies for a Program of Comprehensive Central Nervous System Trauma Centers

Project Directors: Kenneth Shulman, M.D. (Albert Einstein)
Lawrence F. Marshall, M.D. (U.C. at San Diego)
Hubert Rosomoff, M.D. (U. of Miami)
Robert Maxwell, M.D. (U. of Minnesota)
Robert Grossman, M.D. (U. of Texas Med. Branch)
John Jane, M.D. (U. of Virginia)

Current Level of Support: \$ 0 (Albert Einstein)
\$20,087 (U.C. at San Diego)
\$ 0 (U. of Miami)
\$21,517 (U. of Minnesota)
\$16,310 (U. of Texas Med. Branch)
\$25,508 (U. of Virginia)
\$83,422

Objectives: These studies had as their goals:

1. Development of community resources to evaluate the treatment of CNS injured patients in the community and the effects in the community of progress in CNS trauma research.
2. Encouragement of clinical research in the field of CNS trauma.
3. Establishment of methods to bring results of research in CNS trauma rapidly and effectively to the general community.

Major Findings: Work on the feasibility studies progressed well. Epidemiologists and biostatisticians participated in the studies. Community agencies were receptive and with their participation guidelines were produced for long range cooperation.

Significance to NINCDS Program and Biomedical Research: As research in the Head and Spinal Cord Injury Clinical Research Centers has progressed, questions have arisen regarding the applicability of their efforts. Do any of the techniques developed at a particular clinical research center reach the surrounding community hospitals? If so, does their application there produce the same results as it does at the Center? Does the presence of a Center affect the distribution of care of CNS injured patients in a

community? Does the care given in the Center affect mortality or morbidity for a given type of trauma? Should emphasis be on rapid transportation to a Center or to development of local facilities? To answer such questions as these, the Comprehensive CNS Trauma Center Program has been initiated. The results of such community oriented research should be of great value to all organizations involved in the care of the CNS injured patient.

Proposed Course: These contracts terminated on April 30, 1979. An RFP for Comprehensive Central Nervous System Trauma Centers was issued on November 20, 1978. Eleven applications were received. Three were found to be in the zone of consideration and negotiations are presently being conducted in expectation of making awards in FY 79.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1978 -- June 30, 1979

UNIVERSITY OF MARYLAND (N01-NS-7-2358)

Title: Functional Recovery in Rats after Spinal Cord Lesion

Contractor's Project Director: Lloyd Guth, M.D.

Current Level of Support: \$86,337 (awarded in FY 78)

Objective: To replicate and evaluate the research on regeneration and recovery of function of the severed rat spinal cord which was performed by L.A. Matinian and A.S. Andreasian, Orbelli Institute of Physiology, Academy of Sciences of the Armenian Soviet Socialist Republic, Yerevan, USSR, 1973. Enzyme Therapy in Organic Lesions of the Spinal Cord. Akademia Nauk Armenian SSR, 1973 pps. 1-94. In Russian with English summary.

Major Findings: Extensive efforts by the Contractor over a 2-year period to verify the published claims of beneficial effects of enzymes in recovery of function in the transected rat spinal cord by Matinian have been completely unsuccessful. The results are being published.

Significance to NINCDS Program and Biomedical Research: The work of Matinian and Andreasian, if confirmed, has immense potential benefits to the treatment of the severely traumatized spinal cord, and therefore to the possible recovery of paralyzed victims of CNS injury.

Proposed Course: The contract ended June 30, 1979 with the completion of experiments, preparation of reports and submission of results for publication.

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